

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
19 December 2002 (19.12.2002)

PCT

(10) International Publication Number  
**WO 02/101075 A2**

(51) International Patent Classification<sup>7</sup>: **C12Q**

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(21) International Application Number: PCT/US02/18638

(22) International Filing Date: 12 June 2002 (12.06.2002)

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(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
60/298,159 13 June 2001 (13.06.2001) US  
60/298,155 13 June 2001 (13.06.2001) US  
60/335,936 14 November 2001 (14.11.2001) US

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

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(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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**Published:**

— *without international search report and to be republished upon receipt of that report*

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: NOVEL GENES, COMPOSITIONS, KITS, AND METHODS FOR IDENTIFICATION, ASSESSMENT, PREVENTION, AND THERAPY OF CERVICAL CANCER

(57) Abstract: The invention relates to newly discovered nucleic acid molecules and proteins associated with cervical cancer including pre-malignant conditions such as dysplasia. Compositions, kits, and methods for detecting, characterizing, preventing, and treating human cervical cancers are provided.



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NOVEL GENES, COMPOSITIONS, KITS, AND METHODS FOR  
IDENTIFICATION, ASSESSMENT, PREVENTION, AND THERAPY OF  
CERVICAL CANCER

5 RELATED APPLICATIONS

The present application claims priority to U.S. provisional patent application serial no. 60/298,159, filed on June 13, 2001, U.S. provisional patent application serial no. 60/298,155, filed on June 13, 2001, and U.S. provisional patent application serial no. 60/335,936, filed on November 14, 2001, all of which are expressly incorporated by  
10 reference.

FIELD OF THE INVENTION

The field of the invention is cervical cancer, including diagnosis, characterization, management, and therapy of cervical cancer.

15

BACKGROUND OF THE INVENTION

The increased number of cancer cases reported in the United States, and, indeed, around the world, is a major concern. Currently there are only a handful of treatments available for specific types of cancer, and these provide no absolute guarantee  
20 of success. In order to be most effective, these treatments require not only an early detection of the malignancy, but a reliable assessment of the severity of the malignancy.

Cancer of the cervix is one of the most common malignancies in women and remains a significant public health problem throughout the world. In the United States alone, invasive cervical cancer accounts for approximately 19% of all  
25 gynecological cancers. In 1996, it was estimated that there were 14,700 newly diagnosed cases and 4900 deaths attributed to this disease (American Cancer Society, Cancer Facts & Figures 1996, Atlanta, Ga.: American Cancer Society, 1996). In many developing countries, where mass screening programs are not widely available, the clinical problem is more serious. Worldwide, the number of new cases is estimated to be 471,000 with a  
30 four-year survival rate of only 40% (Munoz et al., 1989, *Epidemiology of Cervical Cancer* In: "Human Papillomavirus", New York, Oxford Press, pp 9-39; National Institutes of Health, Consensus Development Conference Statement on Cervical Cancer, Apr.1-3, 1996).



The precursor to cervical cancer is dysplasia, also known in the art as cervical intraepithelial neoplasia (CIN) or squamous intraepithelial lesions (SIL). While it is not understood how normal cells become transformed, the concept of a continuous spectrum of histopathological change from normal, stratified epithelium through CIN to  
5 invasive cancer has been widely accepted for many years. A large body of epidemiological and molecular biological evidence has established human papillomavirus (HPV) infection as a causative factor in cervical cancer. HPV is found in 85% or more of squamous cell invasive lesions, which represent the most common histologic type seen in cervical carcinoma. Additional cofactors have also been  
10 identified, including oncogenes that have been activated by point mutations and chromosomal translocations or deletions.

In light of this, cervical cancer remains a highly preventable form of cancer when pre-invasive lesions are detected early. Cytological examination of Papanicolaou-stained cervical smears (also referred to as Pap smears) is currently the  
15 principle method for detecting cervical cancer. Not surprisingly, the effectiveness of Pap smear screening varies depending not only upon the quality of the sample being used, but also upon subjective parameters that are inherent to the analysis. In addition, despite the historical success of the test, concerns have arisen regarding its ability to reliably predict the behavior of some pre-invasive lesions (Ostor *et al.*, 1993, *Int. J. Gynecol.*  
20 *Pathol.* 12: 186-192; and Genest *et al.*, 1993, *Human Pathol.* 24: 730-736).

#### SUMMARY OF THE INVENTION

The invention relates to cancer markers (hereinafter "markers" or "markers of the inventions"), which are listed in Table 1. The invention provides  
25 nucleic acids and proteins that are encoded by or correspond to the markers (hereinafter "marker nucleic acids" and "marker proteins," respectively). Table 1 provides the sequence identifiers of the sequences of such marker nucleic acids and proteins listed in the accompanying Sequence Listing. The invention further provides antibodies, antibody derivatives and antibody fragments which bind specifically with such proteins  
30 and/or fragments of the proteins.

The invention also relates to various methods, reagents and kits for diagnosing, staging, prognosing, monitoring and treating cervical cancer. "Cervical cancer" as used herein includes carcinomas, (*e.g.*, carcinoma in situ, invasive

carcinoma, metastatic carcinoma) and pre-malignant conditions, (*e.g.*, dysplasia, including CIN or SIL). In one embodiment, the invention provides a diagnostic method of assessing whether a patient has cervical cancer or has higher than normal risk for developing cervical cancer, comprising the steps of comparing the level of expression of  
5 a marker of the invention in a patient sample and the normal level of expression of the marker in a control, *e.g.*, a sample from a patient without cervical cancer. A significantly higher level of expression of the marker in the patient sample as compared to the normal level is an indication that the patient is afflicted with cervical cancer or has higher than normal risk for developing cervical cancer.

10 According to the invention, the markers are selected such that the positive predictive value of the methods of the invention is at least about 10%, preferably about 25%, more preferably about 50% and most preferably about 90%. Also preferred for use in the methods of the invention are markers that are differentially expressed, as compared to normal cervical cells, by at least two-fold in at least about 20%, more  
15 preferably about 50% and most preferably about 75% of any of the following conditions: stage 0 cervical cancer patients, stage I cervical cancer patients, stage II cervical cancer patients, stage III cervical cancer patients, stage IV cervical cancer patients, grade I cervical cancer patients, grade II cervical cancer patients, grade III cervical cancer patients, squamous cell (epidermoid) cervical cancer patients, cervical adenocarcinoma  
20 patients, cervical adenosquamous carcinoma patients, small-cell cervical carcinoma patients, malignant cervical cancer patients, patients with primary carcinomas of the cervix, patients with primary malignant lymphomas of the cervix and patients with secondary malignant lymphomas of the cervix, and all other types of cancers, malignancies and transformations associated with the cervix.

25 In a preferred diagnostic method of assessing whether a patient is afflicted with cervical cancer (*e.g.*, new detection ("screening"), detection of recurrence, reflex testing), the method comprises comparing:  
a) the level of expression of a marker of the invention in a patient sample,  
and  
30 b) the normal level of expression of the marker in a control non-cervical cancer sample.

A significantly higher level of expression of the marker in the patient sample as compared to the normal level is an indication that the patient is afflicted with cervical cancer.

The invention also provides diagnostic methods for assessing the efficacy  
5 of a therapy for inhibiting cervical cancer in a patient. Such methods comprise comparing:

- a) expression of a marker of the invention in a first sample obtained from the patient prior to providing at least a portion of the therapy to the patient, and
- 10 b) expression of the marker in a second sample obtained from the patient following provision of the portion of the therapy.

A significantly lower level of expression of the marker in the second sample relative to that in the first sample is an indication that the therapy is efficacious for inhibiting cervical cancer in the patient.

15 It will be appreciated that in these methods the "therapy" may be any therapy for treating cervical cancer including, but not limited to, chemotherapy, radiation therapy, surgical removal of tumor tissue, gene therapy and biologic therapy such as the administering of antibodies and chemokines. Thus, the methods of the invention may be used to evaluate a patient before, during and after therapy, for  
20 example, to evaluate the reduction in tumor burden.

In a preferred embodiment, the diagnostic methods are directed to therapy using a chemical or biologic agent. These methods comprise comparing:

- a) expression of a marker of the invention in a first sample obtained from the patient and maintained in the presence of the chemical or biologic  
25 agent, and
- b) expression of the marker in a second sample obtained from the patient and maintained in the absence of the agent.

A significantly lower level of expression of the marker in the second sample relative to that in the first sample is an indication that the agent is efficacious for inhibiting cervical  
30 cancer, in the patient. In one embodiment, the first and second samples can be portions of a single sample obtained from the patient or portions of pooled samples obtained from the patient.

The invention additionally provides a monitoring method for assessing the progression of cervical cancer in a patient, the method comprising:

- a) detecting in a patient sample at a first time point, the expression of a marker of the invention;
- 5       b) repeating step a) at a subsequent time point in time; and
- c) comparing the level of expression detected in steps a) and b), and therefrom monitoring the progression of cervical cancer in the patient.

A significantly higher level of expression of the marker in the sample at the subsequent time point from that of the sample at the first time point is an indication that the cervical cancer has progressed, whereas a significantly lower level of expression is an indication  
10       that the cervical cancer has regressed.

The invention further provides a diagnostic method for determining whether cervical cancer has metastasized or is likely to metastasize in the future, the method comprising comparing:

- 15       a) the level of expression of a marker of the invention in a patient sample, and
- b) the normal level (or non-metastatic level) of expression of the marker in a control sample.

A significantly higher level of expression in the patient sample as compared to the  
20       normal level (or non-metastatic level) is an indication that the cervical cancer has metastasized or is likely to metastasize in the future.

The invention moreover provides a test method for selecting a composition for inhibiting cervical cancer in a patient. This method comprises the steps of:

- 25       a) obtaining a sample comprising cancer cells from the patient;
- b) separately maintaining aliquots of the sample in the presence of a plurality of test compositions;
- c) comparing expression of a marker of the invention in each of the aliquots; and
- 30       d) selecting one of the test compositions which significantly reduces the level of expression of the marker in the aliquot containing that test composition, relative to the levels of expression of the marker in the presence of the other test compositions.

The invention additionally provides a test method of assessing the cervical carcinogenic potential of a compound. This method comprises the steps of:

- a) maintaining separate aliquots of cervical cells in the presence and absence of the compound; and
- 5        b) comparing expression of a marker of the invention in each of the aliquots.

A significantly higher level of expression of the marker in the aliquot maintained in the presence of the compound, relative to that of the aliquot maintained in the absence of the compound, is an indication that the compound possesses cervical carcinogenic potential.

- 10        In addition, the invention further provides a method of inhibiting cervical cancer in a patient. This method comprises the steps of:

- a) obtaining a sample comprising cancer cells from the patient;
- b) separately maintaining aliquots of the sample in the presence of a plurality of compositions;
- 15        c) comparing expression of a marker of the invention in each of the aliquots; and
- d) administering to the patient at least one of the compositions which significantly lowers the level of expression of the marker in the aliquot containing that composition, relative to the levels of expression of the marker in the presence of the other compositions.
- 20        In the aforementioned methods, the samples or patient samples comprise cells obtained from the patient. The cells may be found in a cervical smear collected, for example, by a cervical brush. In another embodiment, the sample is a body fluid. Such fluids include, for example, blood fluids, lymph, ascitic fluids, gynecological fluids, urine, and fluids collected by vaginal rinsing. In a further embodiment, the patient

25        sample is *in vivo*.

According to the invention, the level of expression of a marker of the invention in a sample can be assessed, for example, by detecting the presence in the sample of:

- 30        • the corresponding marker protein (*e.g.*, a protein having one of the sequences set forth as "SEQ ID NO (AAs)" in Table 1, or a fragment of the protein (*e.g.* by using a reagent, such as an antibody, an antibody derivative,

an antibody fragment or single-chain antibody, which binds specifically with the protein or protein fragment)

- the corresponding marker nucleic acid (*e.g.* a nucleotide transcript having one of the nucleic acid sequences set forth as “SEQ ID NO (nts)” in Table 1, or a complement thereof), or a fragment of the nucleic acid (*e.g.* by contacting transcribed polynucleotides obtained from the sample with a substrate having affixed thereto one or more nucleic acids having the entire or a segment of the nucleic acid sequence of any of the SEQ ID NO (nts), or a complement thereof)
- a metabolite which is produced directly (*i.e.*, catalyzed) or indirectly by the corresponding marker protein.

According to the invention, any of the aforementioned methods may be performed using a plurality (*e.g.* 2, 3, 5, or 10 or more) of cervical cancer markers, including cervical cancer markers known in the art. In such methods, the level of expression in the sample of each of a plurality of markers, at least one of which is a marker of the invention, is compared with the normal level of expression of each of the plurality of markers in samples of the same type obtained from control humans not afflicted with cervical cancer. A significantly altered (*i.e.*, increased or decreased as specified in the above-described methods using a single marker) level of expression in the sample of one or more markers of the invention, or some combination thereof, relative to that marker's corresponding normal or control level, is an indication that the patient is afflicted with cervical cancer. For all of the aforementioned methods, the marker(s) are preferably selected such that the positive predictive value of the method is at least about 10%.

In a further aspect, the invention provides an antibody, an antibody derivative, or an antibody fragment, which binds specifically with a marker protein (*e.g.*, a protein having one of the amino acid sequences set forth in the Sequence Listing) or a fragment of the protein. The invention also provides methods for making such antibody, antibody derivative, and antibody fragment. Such methods may comprise immunizing a mammal with a protein or peptide comprising the entirety, or a segment of 10 or more amino acids, of a marker protein (*e.g.*, a protein having one of the amino acid sequences set forth in the Sequence Listing), wherein the protein or peptide may be obtained from a cell or by chemical synthesis. The methods of the invention also encompass producing

monoclonal and single-chain antibodies, which would further comprise isolating splenocytes from the immunized mammal, fusing the isolated splenocytes with an immortalized cell line to form hybridomas, and screening individual hybridomas for those that produce an antibody that binds specifically with a marker protein or a  
5 fragment of the protein.

In another aspect, the invention relates to various diagnostic and test kits. In one embodiment, the invention provides a kit for assessing whether a patient is afflicted with cervical cancer. The kit comprises a reagent for assessing expression of a marker of the invention. In another embodiment, the invention provides a kit for  
10 assessing the suitability of a chemical or biologic agent for inhibiting cervical cancer in a patient. Such a kit comprises a reagent for assessing expression of a marker of the invention, and may also comprise one or more of such agents. In a further embodiment, the invention provides kits for assessing the presence of cervical cancer cells or treating cervical cancers. Such kits comprise an antibody, an antibody derivative, or an antibody  
15 fragment, which binds specifically with a marker protein, or a fragment of the protein. Such kits may also comprise a plurality of antibodies, antibody derivatives, or antibody fragments wherein the plurality of such antibody agents binds specifically with a marker protein, or a fragment of the protein.

In an additional embodiment, the invention also provides a kit for  
20 assessing the presence of cervical cancer cells, wherein the kit comprises a nucleic acid probe that binds specifically with a marker nucleic acid or a fragment of the nucleic acid. The kit may also comprise a plurality of probes, wherein each of the probes binds specifically with a marker nucleic acid, or a fragment of the nucleic acid.

In a further aspect, the invention relates to methods for treating a patient  
25 afflicted with cervical cancer or at risk of developing cervical cancer. Such methods may comprise reducing the expression and/or interfering with the biological function of a marker of the invention. In one embodiment, the method comprises providing to the patient an antisense oligonucleotide or polynucleotide complementary to a marker nucleic acid, or a segment thereof. For example, an antisense polynucleotide may be  
30 provided to the patient through the delivery of a vector that expresses an anti-sense polynucleotide of a marker nucleic acid or a fragment thereof. In another embodiment, the method comprises providing to the patient an antibody, an antibody derivative, or antibody fragment, which binds specifically with a marker protein or a fragment of the

protein. In a preferred embodiment, the antibody, antibody derivative or antibody fragment binds specifically with a protein having one of the amino acid sequences set forth in the Sequence Listing, or a fragment of the protein.

It will be appreciated that the methods and kits of the present invention  
5 may also include known cancer markers including known cervical cancer markers. It will further be appreciated that the methods and kits may be used to identify cancers other than cervical cancer.

#### DETAILED DESCRIPTION OF THE INVENTION

10 The invention relates to newly discovered cancer markers associated with the cancerous state of cervical cells. It has been discovered that the higher than normal level of expression of any of these markers or combination of these markers correlates with the presence of cervical cancer including pre-malignant conditions such as dysplasia, in a patient. Methods are provided for detecting the presence of cervical  
15 cancer in a sample, the absence of cervical cancer in a sample, the stage of a cervical cancer, and other characteristics of cervical cancer that are relevant to prevention, diagnosis, characterization, and therapy of cervical cancer in a patient. Methods of treating cervical cancer are also provided.

Table 1 lists the markers of the invention which are over-expressed in  
20 cervical cancer cells compared to normal (*i.e.*, non-cancerous) cervical cells and comprises markers listed in Tables 2 and 3. Table 2 lists newly-identified nucleotide and amino acid sequences. Table 3 lists newly-identified nucleotide sequences. Tables 1-3 provide the sequence listing identifiers of the cDNA sequence of a nucleotide transcript and the amino acid sequence of a protein encoded by or corresponding to each  
25 marker, as well as the location of the protein coding sequence within the cDNA sequence.



Table 1

Marker	Gene Name	SEQ ID NO (nts)	SEQ ID NO (AAs)	CDS
M661	AKAP9: A kinase (PRKA) anchor protein (yotiao) 9, variant 1	1	2	223..11946
M662	AKAP9: A kinase (PRKA) anchor protein (yotiao) 9, variant 2	3	4	223..11922
M663	AKAP9: A kinase (PRKA) anchor protein (yotiao) 9, variant 3	5	6	223..12000
M664	AKAP9: A kinase (PRKA) anchor protein (yotiao) 9, variant 4	7	8	223..11976
M1	APOL1: Apolipoprotein L-I mRNA, splice variant A, major form	9	10	213..1364
M2	APOL1: Apolipoprotein L-I mRNA, splice variant B, minor form	11	12	274..1518
M3	APOL3: apolipoprotein L, 3; TNF-inducible protein CG12-1	13	14	418..1413
OV3	AQP5: Aquaporin 5	15	16	519..1316
M4	BC001980: clone MGC:5618	17	18	157..225
M5	BST2: Bone marrow stromal cell antigen 2	19	20	10..552
M6	BTEB1: basic transcription element binding protein 1	21	22	1265..1999
M665	CD74: CD74 antigen (invariant polypeptide of major histocompatibility complex, class II antigen-associated)	23	24	8..706
M7	CDC20: CDC20 cell cycle protein	25	26	45..1544
M8	CDKN2C: cyclin-dependent kinase inhibitor 2C, p18	27	28	1216..1722
M9	CKTSF1B1: (cysteine knot superfamily 1, BMP antagonist 1), gremlin	29	30	45..1544
M10	CLDN1: claudin 1	31	32	221..856
M11	CLIC4: chloride intracellular channel 4	33	34	198..959
M12	COL1A1: collagen, type I, alpha 1	35	36	120..4514
M13	COL1A2: collagen, type I, alpha 2	37	38	140..4240
M14	COL8A1: collagen, type VIII, alpha 1	39	40	1..2235
M15	COPA: coatamer protein complex, subunit alpha	41	42	467..4141
M16	CRIP1: cysteine-rich protein 1 (intestinal)	43	44	1..234
M17	CTGF: connective tissue growth factor	45	46	146..1195
M18	DOC: downregulated in ovarian cancer 1	47	48	135..2393
M19	EFNA1: ephrin-A1	49	50	74..691
M481	EPPK1: epiplakin 1	51	52	89..15286
M20	FLJ11350: hypothetical protein FLJ11350	53	54	106..1047
M21	FLJ13809: hypothetical protein FLJ13809	55	56	64..1593
M22	FLJ20500: hypothetical protein FLJ20500	57	58	198..896
M23	FLJ23399: hypothetical protein FLJ23399	59	60	283..1770
M24	FN1: Fibronectin 1, variant 1	61	62	<1..2384
M25	FN1: Fibronectin 1, variant 2	63	64	<1..6988
M482	FOSL2: FOS-like antigen 2, variant 1	65	66	324..1304
M483	FOSL2: FOS-like antigen 2, variant 2	67	66	324..1304
M484	FSHPRH1: FSH primary response (LRPR1, rat) homolog 1	68	69	270..2540
M26	FY: Duffy blood group	70	71	495..1511

M485	G1P3:interferon, alpha-inducible protein (clone IFI-6-16)	72	73	108..500
M486	GW112: GW112 protein	74	75	509..1072
M27	HSKERUV: clone 266, Human radiated keratinocyte mRNA 266 (keratin-related protein)	76	77	<1..801
M28	HSPC121: butyrate-induced transcript 1	78	79	150..1271
M29	HUMCLPB: Coactosin like protein	80	81	150..576
M487	hypothetical protein	82	83	58..8163
M30	IFI27: (interferon, alpha-inducible protein 27	84	85	55..423
OV31	IFI30: interferon, gamma-inducible protein 30	86	87	41..952
M31	IFITM2: interferon induced transmembrane protein 2 (1-8D)	88	89	280..678
M32	IGFBP-3: insulin-like growth factor binding protein 3	90	91	133..1009
M33	IL8RA: interleukin 8	92	93	75..374
M34	INHBA: Inhibin, beta-1	94	95	86..1366
M488	ITGA3: integrin, alpha 3 (antigen CD49C, alpha 3 subunit of VLA-3 receptor), variant a	96	97	74..3229
M454	ITGA3: integrin, alpha 3 (antigen CD49C, alpha 3 subunit of VLA-3 receptor), variant b	98	99	74..3274
M35	ITGB6: integrin, beta 6	100	101	195..2561
M36	KATII: L-kynurenine/alpha-aminoadipate aminotransferase	102	103	454..1731
M666	KCNAB1: potassium voltage-gated channel, shaker-related subfamily, beta member 1, variant 1	104	105	89..1315
M667	KCNAB1: potassium voltage-gated channel, shaker-related subfamily, beta member 1, variant 2	106	107	54..1313
M668	KCNAB1: potassium voltage-gated channel, shaker-related subfamily, beta member 1, variant 3	108	109	28..1233
M37	KIAA0662: KIAA0662 protein	110	111	<1..2035
M38	LAMA3: Laminin, alpha-3 (nicein (150kD), (kalinin (165kD), BM600 (150kD)	112	113	1..5142
M39	LAMC2: laminin, gamma 2	114	115	90..3671
M40	LSM5: U6 snRNA-associated Sm-like protein	116	117	1..276
M41	LUM: lumican	118	119	85..1101
M42	MACMARCKS: macrophage myristoylated alanine-rich C kinase substrate	120	121	14..601
M43	MAGP: microfibrillar-associated protein 2 precursor, transcript variant 1	122	123	115..666
M44	MAGP: microfibrillar-associated protein 2 precursor, transcript variant 2	124	125	100..651
M45	MAPK: mitogen-activated protein kinase 1	126	127	328..1410
M489	MCM6: minichromosome maintenance deficient (mis5, S. pombe) 6	128	129	62..2527
M46	MDK: midkine (neurite growth-promoting factor 2)	130	131	26..457
M47	MGP: matrix Gla protein	132	133	47..358
M48	MMP12: matrix metalloproteinase 12	134	135	13..1425
M49	MMP3: matrix metalloproteinase 3, stromelysin 1, progelatinase	136	137	64..1497
M294	MMP7: matrix metalloproteinase 7 (matrilysin, uterine), PUMP1 proteinase, variant 1	138	139	48..851
OV52	MMP7: matrix metalloproteinase 7 (matrilysin, uterine), PUMP1 proteinase, variant 2	140	139	28..831

M50	MMP9: matrix metalloproteinase 9, gelatinase B, 92kD gelatinase, 92kD type IV collagenase	141	142	20..2143
OV68	MSLN: mesothelin, variant 1	143	144	88..2196
OV69	MSLN: mesothelin, variant 2	145	146	88..1980
OV70	MSLN: mesothelin, variant 3	147	148	88..1950
OV71	MSLN: mesothelin, variant 4	149	150	88..2172
OV72	MSLN: mesothelin, variant 5	151	152	88..1926
OV43	MSLN: mesothelin, variant 6	153	154	88..1956
OV45	MUC1: mucin 1, transmembrane, variant 1	155	156	58..1605
M669	MUC1: mucin 1, transmembrane, variant 2	157	158	74..3841
M51	MYBL2: v-myb avian myeloblastosis viral oncogene homolog-like 2	159	160	128..2230
M52	MYH11: smooth muscle myosin heavy chain 11, isoform SM1	161	162	89..6007
M53	MYH11: smooth muscle myosin heavy chain 11, isoform SM2	163	164	89..5905
M54	NK4: natural killer cell transcript 4, variant 1	165	166	60..764
M670	NK4: natural killer cell transcript 4, variant 2	167	168	60..764
M55	NP25: (neuronal protein)	169	170	50..898
OV48	OPN-a (osteopontin), SPP1 (secreted phosphoprotein 1), bone sialoprotein I	171	172	1..942
OV49	OPN-b (osteopontin), SPP1 (secreted phosphoprotein 1), bone sialoprotein I	173	174	88..990
OV50	OPN-c (osteopontin), SPP1 (secreted phosphoprotein 1), bone sialoprotein I	175	176	1..861
M56	OSF-2, osteoblast specific factor 2 (fascin-like), variant 1	177	178	12..2522
M491	OSF-2, osteoblast specific factor 2 (fascin-like), variant 2	179	180	28..2367
M57	PIM2: pim-2 oncogene	181	182	186..1190
M58	PLAU: plasminogen activator, urokinase	183	184	77..1372
M59	PLK: polo (Drosophila)-like kinase	185	186	64..1875
M671	PNN: pinin, desmosome associated protein	187	188	31..2262
M60	PRG1: proteoglycan 1, secretory granule	189	190	25..501
M61	PTH1H: parathyroid hormone-like hormone	191	192	304..831
M62	PTN: pleiotrophin (heparin binding growth factor 8, neurite growth-promoting factor 1)	193	194	1542..2048
M63	RAB6KIFL: RAB6 interacting, kinesin-like (rabkinesin6)	195	196	28..2700
M64	RARRES3: retinoic acid receptor responder (tazarotene induced) 3	197	198	62..556
M65	RBP1: retinol-binding protein 1 (cellular), CRABP-I, CRBP-I	199	200	126..533
M66	RGS16: Regulator of G protein signaling-16	201	202	93..701
M67	S100A2: S100 calcium binding protein A2, variant 1	203	204	72..362
M68	S100A2: S100 calcium binding protein A2, variant 2	205	206	41..334
M69	SCYA20: small inducible cytokine subfamily A (Cys-Cys), member 20	207	208	59..349
M70	SPARC: Osteonectin (secreted protein, acidic, cysteine-rich)	209	210	58..969
M71	STCH: stress 70 protein chaperone, microsome-associated	211	212	37..1452
M492	STK12: serine/ threonine kinase 12	213	214	58..1092

M72	TK1: thymidine kinase 1, soluble	215	216	58..762
OV86	TMPRSS4: transmembrane protease, serine 4	217	218	310..1623
M73	TMSB4X: thymosin, beta 4, X chromosome	219	220	78..212
M74	TOP2A: topoisomerase (DNA) II alpha (170kD)	221	222	37..4632
M493	TPM1: tropomyosin 1 (alpha)	223	224	57..911
M75	TXN: thioredoxin	225	226	64..381
M76	UBCH10: ubiquitin carrier protein E2-C	227	228	41..580
M77	UBD: diubiquitin	229	230	19..516
M78	unnamed gene (1)	231	232	45..1353
M79	unnamed gene (2)	233	234	1..1508
M80	VATD: vacuolar proton pump delta polypeptide	235	236	166..909
M81	ZWINT: ZW10 interactor	237	238	25..858

Table 2

Marker	Gene Name	SEQ ID NO (nts)	SEQ ID NO (AAs)	CDS
M661	AKAP9: A kinase (PRKA) anchor protein (yotiao) 9, variant 1	1	2	223..1194 6
M662	AKAP9: A kinase (PRKA) anchor protein (yotiao) 9, variant 2	3	4	223..1192 2
M663	AKAP9: A kinase (PRKA) anchor protein (yotiao) 9, variant 3	5	6	223..1200 0
M664	AKAP9: A kinase (PRKA) anchor protein (yotiao) 9, variant 4	7	8	223..1197 6
OV68	MSLN: mesothelin, variant 1	143	144	88..2196
OV69	MSLN: mesothelin, variant 2	145	146	88..1980
OV70	MSLN: mesothelin, variant 3	147	148	88..1950
OV71	MSLN: mesothelin, variant 4	149	150	88..2172
OV72	MSLN: mesothelin, variant 5	151	152	88..1926
M670	NK4: natural killer cell transcript 4, variant 2	167	168	60..764
M67	S100A2: S100 calcium binding protein A2, variant 1	203	204	72..362
OV86	TMPRSS4: transmembrane protease, serine 4	217	218	310..1623
M78	unnamed gene (1)	231	232	45..1353
M79	unnamed gene (2)	233	234	1..1508

Table 3

Marker	Gene Name	SEQ ID NO (nts)	SEQ ID NO (AAs)	CDS
M481	EPPK1: epiplakin 1	51	52	89..15286
M482	FOSL2: FOS-like antigen 2, variant 1	65	66	324..1304
M483	FOSL2: FOS-like antigen 2, variant 2	67	66	324..1304
M484	FSHPRH1: FSH primary response (LRPR1, rat) homolog 1	68	69	270..2540
M35	ITGB6: integrin, beta 6	100	101	195..2561
OV43	MSLN: mesothelin, variant 6	153	154	88..1956

### Definitions

5 As used herein, each of the following terms has the meaning associated with it in this section.

The articles "a" and "an" are used herein to refer to one or to more than one (*i.e.* to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

10 A "marker" is a gene whose altered level of expression in a tissue or cell from its expression level in normal or healthy tissue or cell is associated with a disease state, such as cancer. A "marker nucleic acid" is a nucleic acid (*e.g.*, mRNA, cDNA) encoded by or corresponding to a marker of the invention. Such marker nucleic acids include DNA (*e.g.*, cDNA) comprising the entire or a partial sequence of any of the  
15 nucleic acid sequences set forth in the Sequence Listing or the complement of such a sequence. The marker nucleic acids also include RNA comprising the entire or a partial sequence of any of the nucleic acid sequences set forth in the Sequence Listing or the complement of such a sequence, wherein all thymidine residues are replaced with uridine residues. A "marker protein" is a protein encoded by or corresponding to a  
20 marker of the invention. A marker protein comprises the entire or a partial sequence of any of the sequences set forth in the Sequence Listing. The terms "protein" and "polypeptide" are used interchangeably.

The term "probe" refers to any molecule which is capable of selectively binding to a specifically intended target molecule, for example, a nucleotide transcript or  
25 protein encoded by or corresponding to a marker. Probes can be either synthesized by one skilled in the art, or derived from appropriate biological preparations. For purposes of detection of the target molecule, probes may be specifically designed to be labeled, as

described herein. Examples of molecules that can be utilized as probes include, but are not limited to, RNA, DNA, proteins, antibodies, and organic molecules.

A "cervical-associated" body fluid is a fluid which, when in the body of a patient, contacts or passes through cervical cells or into which cells or proteins shed from cervical cells are capable of passing. The cells may be found in a cervical smear collected, for example, by a cervical brush. Exemplary cervical-associated body fluids include blood fluids, lymph, ascitic fluids, gynecological fluids, cystic fluid, urine, and fluids collected by vaginal rinsing.

The "normal" level of expression of a marker is the level of expression of the marker in cervical cells of a human subject or patient not afflicted with cervical cancer

An "over-expression" or "significantly higher level of expression" of a marker refers to an expression level in a test sample that is greater than the standard error of the assay employed to assess expression, and is preferably at least twice, and more preferably three, four, five or ten times the expression level of the marker in a control sample (*e.g.*, sample from a healthy subjects not having the marker associated disease) and preferably, the average expression level of the marker in several control samples.

A "significantly lower level of expression" of a marker refers to an expression level in a test sample that is at least twice, and more preferably three, four, five or ten times lower than the expression level of the marker in a control sample (*e.g.*, sample from a healthy subject not having the marker associated disease) and preferably, the average expression level of the marker in several control samples.

As used herein, the term "promoter/regulatory sequence" means a nucleic acid sequence which is required for expression of a gene product operably linked to the promoter/regulatory sequence. In some instances, this sequence may be the core promoter sequence and in other instances, this sequence may also include an enhancer sequence and other regulatory elements which are required for expression of the gene product. The promoter/regulatory sequence may, for example, be one which expresses the gene product in a tissue-specific manner.

A "constitutive" promoter is a nucleotide sequence which, when operably linked with a polynucleotide which encodes or specifies a gene product, causes the gene product to be produced in a living human cell under most or all physiological conditions of the cell.

5           An "inducible" promoter is a nucleotide sequence which, when operably linked with a polynucleotide which encodes or specifies a gene product, causes the gene product to be produced in a living human cell substantially only when an inducer which corresponds to the promoter is present in the cell.

10           A "tissue-specific" promoter is a nucleotide sequence which, when operably linked with a polynucleotide which encodes or specifies a gene product, causes the gene product to be produced in a living human cell substantially only if the cell is a cell of the tissue type corresponding to the promoter.

15           A "transcribed polynucleotide" or "nucleotide transcript" is a polynucleotide (*e.g.* an mRNA, hnRNA, a cDNA, or an analog of such RNA or cDNA) which is complementary to or homologous with all or a portion of a mature mRNA made by transcription of a marker of the invention and normal post-transcriptional processing (*e.g.* splicing), if any, of the RNA transcript, and reverse transcription of the RNA transcript.

20           "Complementary" refers to the broad concept of sequence complementarity between regions of two nucleic acid strands or between two regions of the same nucleic acid strand. It is known that an adenine residue of a first nucleic acid region is capable of forming specific hydrogen bonds ("base pairing") with a residue of a second nucleic acid region which is antiparallel to the first region if the residue is thymine or uracil. Similarly, it is known that a cytosine residue of a first nucleic acid strand is capable of base pairing with a residue of a second nucleic acid strand which is antiparallel to the first strand if the residue is guanine. A first region of a nucleic acid is complementary to a second region of the same or a different nucleic acid if, when the two regions are arranged in an antiparallel fashion, at least one nucleotide residue of the first region is capable of base pairing with a residue of the second region. Preferably, 25           the first region comprises a first portion and the second region comprises a second portion, whereby, when the first and second portions are arranged in an antiparallel fashion, at least about 50%, and preferably at least about 75%, at least about 90%, or at least about 95% of the nucleotide residues of the first portion are capable of base pairing 30

with nucleotide residues in the second portion. More preferably, all nucleotide residues of the first portion are capable of base pairing with nucleotide residues in the second portion.

"Homologous" as used herein, refers to nucleotide sequence similarity  
5 between two regions of the same nucleic acid strand or between regions of two different nucleic acid strands. When a nucleotide residue position in both regions is occupied by the same nucleotide residue, then the regions are homologous at that position. A first region is homologous to a second region if at least one nucleotide residue position of each region is occupied by the same residue. Homology between two regions is  
10 expressed in terms of the proportion of nucleotide residue positions of the two regions that are occupied by the same nucleotide residue. By way of example, a region having the nucleotide sequence 5'-ATTGCC-3' and a region having the nucleotide sequence 5'-TATGGC-3' share 50% homology. Preferably, the first region comprises a first portion and the second region comprises a second portion, whereby, at least about 50%, and  
15 preferably at least about 75%, at least about 90%, or at least about 95% of the nucleotide residue positions of each of the portions are occupied by the same nucleotide residue. More preferably, all nucleotide residue positions of each of the portions are occupied by the same nucleotide residue.

A molecule is "fixed" or "affixed" to a substrate if it is covalently or non-  
20 covalently associated with the substrate such the substrate can be rinsed with a fluid (*e.g.* standard saline citrate, pH 7.4) without a substantial fraction of the molecule dissociating from the substrate.

As used herein, a "naturally-occurring" nucleic acid molecule refers to an RNA or DNA molecule having a nucleotide sequence that occurs in an organism found  
25 in nature.

A cancer is "inhibited" if at least one symptom of the cancer is alleviated, terminated, slowed, or prevented. As used herein, cervical cancer is also "inhibited" if recurrence or metastasis of the cancer is reduced, slowed, delayed, or prevented.

A kit is any manufacture (*e.g.* a package or container) comprising at least  
30 one reagent, *e.g.* a probe, for specifically detecting the expression of a marker of the invention. The kit may be promoted, distributed, or sold as a unit for performing the methods of the present invention.



“Proteins of the invention” encompass marker proteins and their fragments; variant marker proteins and their fragments; peptides and polypeptides comprising an at least 15 amino acid segment of a marker or variant marker protein; and fusion proteins comprising a marker or variant marker protein, or an at least 15 amino acid segment of a marker or variant marker protein.

Unless otherwise specified herewithin, the terms “antibody” and “antibodies” broadly encompass naturally-occurring forms of antibodies (*e.g.*, IgG, IgA, IgM, IgE) and recombinant antibodies such as single-chain antibodies, chimeric and humanized antibodies and multi-specific antibodies, as well as fragments and derivatives of all of the foregoing, which fragments and derivatives have at least an antigenic binding site. Antibody derivatives may comprise a protein or chemical moiety conjugated to an antibody.

#### Description

The present invention is based, in part, on newly identified markers which are over-expressed in cervical cancer cells as compared to their expression in normal (*i.e.* non-cancerous) cervical cells. The enhanced expression of one or more of these markers in cervical cells is herein correlated with the cancerous state of the tissue. The invention provides compositions, kits, and methods for assessing the cancerous state of cervical cells (*e.g.* cells obtained from a human, cultured human cells, archived or preserved human cells and *in vivo* cells) as well as treating patients afflicted with cervical cancer.

The compositions, kits, and methods of the invention have the following uses, among others:

- 1) assessing whether a patient is afflicted with cervical cancer;
- 2) assessing the stage of cervical cancer in a human patient;
- 3) assessing the grade of cervical cancer in a patient;
- 4) assessing the benign or malignant nature of cervical cancer in a patient;
- 5) assessing the metastatic potential of cervical cancer in a patient;
- 6) assessing the histological type of neoplasm associated with cervical cancer in a patient;

- 7) making antibodies, antibody fragments or antibody derivatives that are useful for treating cervical cancer and/or assessing whether a patient is afflicted with cervical cancer;
- 8) assessing the presence of cervical cancer cells;
- 5 9) assessing the efficacy of one or more test compounds for inhibiting cervical cancer in a patient;
- 10 10) assessing the efficacy of a therapy for inhibiting cervical cancer in a patient;
- 11) monitoring the progression of cervical cancer in a patient;
- 10 12) selecting a composition or therapy for inhibiting cervical cancer in a patient;
- 13) treating a patient afflicted with cervical cancer;
- 14) inhibiting cervical cancer in a patient;
- 15 15) assessing the cervical carcinogenic potential of a test compound; and
- 16) preventing the onset of cervical cancer in a patient at risk for developing cervical cancer.

The invention thus includes a method of assessing whether a patient is afflicted with cervical cancer which includes assessing whether the patient has pre-  
20 metastasized cervical cancer. This method comprises comparing the level of expression of a marker of the invention (listed in Table 1) in a patient sample and the normal level of expression of the marker in a control, *e.g.*, a non-cervical cancer sample. A significantly higher level of expression of the marker in the patient sample as compared to the normal level is an indication that the patient is afflicted with cervical cancer.

25 Gene delivery vehicles, host cells and compositions (all described herein) containing nucleic acids comprising the entirety, or a segment of 15 or more nucleotides, of any of the nucleic acid sequences set forth in the Sequence Listing, or the complement of such sequences, and polypeptides comprising the entirety, or a segment of 10 or more amino acids, of any of the amino acid sequences set forth in the Sequence  
30 Listing, are also provided by this invention.

As described herein, cervical cancer in patients is associated with an increased level of expression of one or more markers of the invention. While, as discussed above, some of these changes in expression level result from occurrence of the

cervical cancer, others of these changes induce, maintain, and promote the cancerous state of cervical cancer cells. Thus, cervical cancer characterized by an increase in the level of expression of one or more markers of the invention can be inhibited by reducing and/or interfering with the expression of the markers and/or function of the proteins encoded by those markers.

Expression of a marker of the invention can be inhibited in a number of ways generally known in the art. For example, an antisense oligonucleotide can be provided to the cervical cancer cells in order to inhibit transcription, translation, or both, of the marker(s). Alternately, a polynucleotide encoding an antibody, an antibody derivative, or an antibody fragment which specifically binds a marker protein, and operably linked with an appropriate promoter/regulator region, can be provided to the cell in order to generate intracellular antibodies which will inhibit the function or activity of the protein. The expression and/or function of a marker may also be inhibited by treating the cervical cancer cell with an antibody, antibody derivative or antibody fragment that specifically binds a marker protein. Using the methods described herein, a variety of molecules, particularly including molecules sufficiently small that they are able to cross the cell membrane, can be screened in order to identify molecules which inhibit expression of a marker or inhibit the function of a marker protein. The compound so identified can be provided to the patient in order to inhibit cervical cancer cells of the patient.

Any marker or combination of markers of the invention, as well as any known markers in combination with the markers of the invention, may be used in the compositions, kits, and methods of the present invention. In general, it is preferable to use markers for which the difference between the level of expression of the marker in cervical cancer cells and the level of expression of the same marker in normal cervical cells is as great as possible. Although this difference can be as small as the limit of detection of the method for assessing expression of the marker, it is preferred that the difference be at least greater than the standard error of the assessment method, and preferably a difference of at least 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9-, 10-, 15-, 20-, 25-, 100-, 500-, 1000-fold or greater than the level of expression of the same marker in normal cervical tissue.

It is recognized that certain marker proteins are secreted from cervical cells (*i.e.* one or both of normal and cancerous cells) to the extracellular space surrounding the cells. These markers are preferably used in certain embodiments of the compositions, kits, and methods of the invention, owing to the fact that the such marker proteins can be detected in a cervical-associated body fluid sample, which may be more easily collected from a human patient than a tissue biopsy sample. In addition, preferred *in vivo* techniques for detection of a marker protein include introducing into a subject a labeled antibody directed against the protein. For example, the antibody can be labeled with a radioactive marker whose presence and location in a subject can be detected by standard imaging techniques.

It is a simple matter for the skilled artisan to determine whether any particular marker protein is a secreted protein. In order to make this determination, the marker protein is expressed in, for example, a mammalian cell, preferably a human cervical cell line, extracellular fluid is collected, and the presence or absence of the protein in the extracellular fluid is assessed (*e.g.* using a labeled antibody which binds specifically with the protein).

The following is an example of a method which can be used to detect secretion of a protein. About  $8 \times 10^5$  293T cells are incubated at 37°C in wells containing growth medium (Dulbecco's modified Eagle's medium {DMEM} supplemented with 10% fetal bovine serum) under a 5% (v/v) CO<sub>2</sub>, 95% air atmosphere to about 60-70% confluence. The cells are then transfected using a standard transfection mixture comprising 2 micrograms of DNA comprising an expression vector encoding the protein and 10 microliters of LipofectAMINE™ (GIBCO/BRL Catalog no. 18342-012) per well. The transfection mixture is maintained for about 5 hours, and then replaced with fresh growth medium and maintained in an air atmosphere. Each well is gently rinsed twice with DMEM which does not contain methionine or cysteine (DMEM-MC; ICN Catalog no. 16-424- 54). About 1 milliliter of DMEM-MC and about 50 microcuries of Trans-<sup>35</sup>S™ reagent (ICN Catalog no. 51006) are added to each well. The wells are maintained under the 5% CO<sub>2</sub> atmosphere described above and incubated at 37°C for a selected period. Following incubation, 150 microliters of conditioned medium is removed and centrifuged to remove floating cells and debris.

The presence of the protein in the supernatant is an indication that the protein is secreted.

It will be appreciated that patient samples containing cervical cells may be used in the methods of the present invention. In these embodiments, the level of expression of the marker can be assessed by assessing the amount (*e.g.* absolute amount or concentration) of the marker in a cervical cell sample, *e.g.*, cervical smear obtained from a patient. The cell sample can, of course, be subjected to a variety of well-known post-collection preparative and storage techniques (*e.g.*, nucleic acid and/or protein extraction, fixation, storage, freezing, ultrafiltration, concentration, evaporation, centrifugation, etc.) prior to assessing the amount of the marker in the sample. Likewise, cervical smears may also be subjected to post-collection preparative and storage techniques, *e.g.*, fixation.

The compositions, kits, and methods of the invention can be used to detect expression of marker proteins having at least one portion which is displayed on the surface of cells which express it. It is a simple matter for the skilled artisan to determine whether a marker protein, or a portion thereof, is exposed on the cell surface. For example, immunological methods may be used to detect such proteins on whole cells, or well known computer-based sequence analysis methods may be used to predict the presence of at least one extracellular domain (*i.e.* including both secreted proteins and proteins having at least one cell-surface domain). Expression of a marker protein having at least one portion which is displayed on the surface of a cell which expresses it may be detected without necessarily lysing the cell (*e.g.* using a labeled antibody which binds specifically with a cell-surface domain of the protein).

Expression of a marker of the invention may be assessed by any of a wide variety of well known methods for detecting expression of a transcribed nucleic acid or protein. Non-limiting examples of such methods include immunological methods for detection of secreted, cell-surface, cytoplasmic, or nuclear proteins, protein purification methods, protein function or activity assays, nucleic acid hybridization methods, nucleic acid reverse transcription methods, and nucleic acid amplification methods.

In a preferred embodiment, expression of a marker is assessed using an antibody (*e.g.* a radio-labeled, chromophore-labeled, fluorophore-labeled, or enzyme-labeled antibody), an antibody derivative (*e.g.* an antibody conjugated with a substrate or with the protein or ligand of a protein-ligand pair {*e.g.* biotin-streptavidin} ), or an

antibody fragment (*e.g.* a single-chain antibody, an isolated antibody hypervariable domain, etc.) which binds specifically with a marker protein or fragment thereof, including a marker protein which has undergone all or a portion of its normal post-translational modification.

5                   In another preferred embodiment, expression of a marker is assessed by preparing mRNA/cDNA (*i.e.* a transcribed polynucleotide) from cells in a patient sample, and by hybridizing the mRNA/cDNA with a reference polynucleotide which is a complement of a marker nucleic acid, or a fragment thereof. cDNA can, optionally, be amplified using any of a variety of polymerase chain reaction methods prior to  
10 hybridization with the reference polynucleotide; preferably, it is not amplified. Expression of one or more markers can likewise be detected using quantitative PCR to assess the level of expression of the marker(s). Alternatively, any of the many known methods of detecting mutations or variants (*e.g.* single nucleotide polymorphisms, deletions, etc.) of a marker of the invention may be used to detect occurrence of a  
15 marker in a patient.

                  In a related embodiment, a mixture of transcribed polynucleotides obtained from the sample is contacted with a substrate having fixed thereto a polynucleotide complementary to or homologous with at least a portion (*e.g.* at least 7, 10, 15, 20, 25, 30, 40, 50, 100, 500, or more nucleotide residues) of a marker nucleic  
20 acid. If polynucleotides complementary to or homologous with are differentially detectable on the substrate (*e.g.* detectable using different chromophores or fluorophores, or fixed to different selected positions), then the levels of expression of a plurality of markers can be assessed simultaneously using a single substrate (*e.g.* a "gene chip" microarray of polynucleotides fixed at selected positions). When a method of  
25 assessing marker expression is used which involves hybridization of one nucleic acid with another, it is preferred that the hybridization be performed under stringent hybridization conditions.

                  Because the compositions, kits, and methods of the invention rely on detection of a difference in expression levels of one or more markers of the invention, it  
30 is preferable that the level of expression of the marker is significantly greater than the minimum detection limit of the method used to assess expression in at least one of normal cervical cells and cancerous cervical cells.

It is understood that by routine screening of additional patient samples using one or more of the markers of the invention, it will be realized that certain of the markers are over-expressed in cancers of various types, including specific cervical cancers, as well as other cancers such as breast cancer, ovarian cancer, etc. For example, it will be confirmed that some of the markers of the invention are over-expressed in most (*i.e.* 50% or more) or substantially all (*i.e.* 80% or more) of cervical cancer. Furthermore, it will be confirmed that certain of the markers of the invention are associated with cervical cancer of various stages (*i.e.* stage 0, I, II, III, and IV cervical cancers, as well as subclassifications IA1, IA2, IB, IB1, IB2, IIA, IIB, IIIA, IIIB, IVA, and IVB, using the FIGO Stage Grouping system for primary carcinoma of the cervix (see *Gynecologic Oncology*, 1991, 41:199 and *Cancer*, 1992, 69:482)), and pre-malignant conditions (*e.g.*, dysplasia including CIN or SIL), of various histologic subtypes (*e.g.* squamous cell carcinomas and squamous cell carcinoma variants such as verrucous carcinoma, lymphoepithelioma-like carcinoma, papillary squamous neoplasm and spindle cell squamous cell carcinoma (see *Cervical Cancer and Preinvasive Neoplasia*, 1996, pp. 90-91) serous, mucinous, endometrioid, and clear cell subtypes, as well as subclassifications and alternate classifications adenocarcinoma, papillary adenocarcinoma, papillary cystadenocarcinoma, surface papillary carcinoma, malignant adenofibroma, cystadenofibroma, adenocarcinoma, cystadenocarcinoma, adenoacanthoma, endometrioid stromal sarcoma, mesodermal {Müllerian} mixed tumor, malignant carcinoma, Brenner tumor, mixed epithelial tumor, and undifferentiated carcinoma, using the WHO/FIGO system for classification of malignant cervical tumors; Scully, *Atlas of Tumor Pathology*, 3d series, Washington DC), and various grades (*i.e.* grade I {well differentiated} , grade II {moderately well differentiated}, and grade III {poorly differentiated from surrounding normal tissue} ). In addition, as a greater number of patient samples are assessed for expression of the markers of the invention and the outcomes of the individual patients from whom the samples were obtained are correlated, it will also be confirmed that altered expression of certain of the markers of the invention are strongly correlated with malignant cancers and that altered expression of other markers of the invention are strongly correlated with benign tumors. The compositions, kits, and methods of the invention are thus useful for characterizing one or more of the stage, grade, histological type, and benign/malignant nature of cervical cancer in patients.

When the compositions, kits, and methods of the invention are used for characterizing one or more of the stage, grade, histological type, and benign/malignant nature of cervical cancer in a patient, it is preferred that the marker or panel of markers of the invention is selected such that a positive result is obtained in at least about 20%,  
5 and preferably at least about 40%, 60%, or 80%, and more preferably in substantially all patients afflicted with a cervical cancer of the corresponding stage, grade, histological type, or benign/malignant nature. Preferably, the marker or panel of markers of the invention is selected such that a positive predictive value (PPV) of greater than about 10% is obtained for the general population (more preferably coupled with an assay  
10 specificity greater than 80%).

When a plurality of markers of the invention are used in the compositions, kits, and methods of the invention, the level of expression of each marker in a patient sample can be compared with the normal level of expression of each of the plurality of markers in non-cancerous samples of the same type, either in a single  
15 reaction mixture (*i.e.* using reagents, such as different fluorescent probes, for each marker) or in individual reaction mixtures corresponding to one or more of the markers. In one embodiment, a significantly increased level of expression of more than one of the plurality of markers in the sample, relative to the corresponding normal levels, is an indication that the patient is afflicted with cervical cancer. When a plurality of markers  
20 is used, it is preferred that 2, 3, 4, 5, 8, 10, 12, 15, 20, 30, or 50 or more individual markers be used, wherein fewer markers are preferred.

In order to maximize the sensitivity of the compositions, kits, and methods of the invention (*i.e.* by interference attributable to cells of non-cervical origin in a patient sample), it is preferable that the marker of the invention used therein be a  
25 marker which has a restricted tissue distribution, *e.g.*, normally not expressed in a non-cervical tissue.

Only a small number of markers are known to be associated with cervical cancer (*e.g.* bcl-2, 15A8 antigen, cdc6, Mcm5, and EGFR). These markers are not, of course, included among the markers of the invention, although they may be used  
30 together with one or more markers of the invention in a panel of markers, for example. It is well known that certain types of genes, such as oncogenes, tumor suppressor genes, growth factor-like genes, protease-like genes, and protein kinase-like genes are often involved with development of cancers of various types. Thus, among the markers of the



invention, use of those which correspond to proteins which resemble known proteins encoded by known oncogenes and tumor suppressor genes, and those which correspond to proteins which resemble growth factors, proteases, and protein kinases are preferred.

It is recognized that the compositions, kits, and methods of the invention  
5 will be of particular utility to patients having an enhanced risk of developing cervical cancer and their medical advisors. Patients recognized as having an enhanced risk of developing cervical cancer include, for example, patients having a familial history of cervical cancer, patients identified as having a mutant oncogene (*i.e.* at least one allele), and patients of advancing age (*i.e.* women older than about 50 or 60 years).

10 The level of expression of a marker in normal (*i.e.* non-cancerous) human cervical tissue can be assessed in a variety of ways. In one embodiment, this normal level of expression is assessed by assessing the level of expression of the marker in a portion of cervical cells which appears to be non-cancerous and by comparing this normal level of expression with the level of expression in a portion of the cervical cells  
15 which is suspected of being cancerous. Alternately, and particularly as further information becomes available as a result of routine performance of the methods described herein, population-average values for normal expression of the markers of the invention may be used. In other embodiments, the 'normal' level of expression of a marker may be determined by assessing expression of the marker in a patient sample  
20 obtained from a non-cancer-afflicted patient, from a patient sample obtained from a patient before the suspected onset of cervical cancer in the patient, from archived patient samples, and the like.

The invention includes compositions, kits, and methods for assessing the presence of cervical cancer cells in a sample (*e.g.* an archived tissue sample or a sample  
25 obtained from a patient). These compositions, kits, and methods are substantially the same as those described above, except that, where necessary, the compositions, kits, and methods are adapted for use with samples other than patient samples. For example, when the sample to be used is a paraffinized, archived human tissue sample, it can be necessary to adjust the ratio of compounds in the compositions of the invention, in the  
30 kits of the invention, or the methods used to assess levels of marker expression in the sample. Such methods are well known in the art and within the skill of the ordinary artisan.

The invention includes a kit for assessing the presence of cervical cancer cells (*e.g.* in a sample such as a patient sample). The kit comprises a plurality of reagents, each of which is capable of binding specifically with a marker nucleic acid or protein. Suitable reagents for binding with a marker protein include antibodies, antibody derivatives, antibody fragments, and the like. Suitable reagents for binding with a marker nucleic acid (*e.g.* a genomic DNA, an mRNA, a spliced mRNA, a cDNA, or the like) include complementary nucleic acids. For example, the nucleic acid reagents may include oligonucleotides (labeled or non-labeled) fixed to a substrate, labeled oligonucleotides not bound with a substrate, pairs of PCR primers, molecular beacon probes, and the like.

The kit of the invention may optionally comprise additional components useful for performing the methods of the invention. By way of example, the kit may comprise fluids (*e.g.* SSC buffer) suitable for annealing complementary nucleic acids or for binding an antibody with a protein with which it specifically binds, one or more sample compartments, an instructional material which describes performance of a method of the invention, a sample of normal cervical cells, a sample of cervical cancer cells, and the like.

The invention also includes a method of making an isolated hybridoma which produces an antibody useful for assessing whether patient is afflicted with an cervical cancer. In this method, a protein or peptide comprising the entirety or a segment of a marker protein is synthesized or isolated (*e.g.* by purification from a cell in which it is expressed or by transcription and translation of a nucleic acid encoding the protein or peptide *in vivo* or *in vitro* using known methods). A vertebrate, preferably a mammal such as a mouse, rat, rabbit, or sheep, is immunized using the protein or peptide. The vertebrate may optionally (and preferably) be immunized at least one additional time with the protein or peptide, so that the vertebrate exhibits a robust immune response to the protein or peptide. Splenocytes are isolated from the immunized vertebrate and fused with an immortalized cell line to form hybridomas, using any of a variety of methods well known in the art. Hybridomas formed in this manner are then screened using standard methods to identify one or more hybridomas which produce an antibody which specifically binds with the marker protein or a fragment thereof. The invention also includes hybridomas made by this method and antibodies made using such hybridomas.

The invention also includes a method of assessing the efficacy of a test compound for inhibiting cervical cancer cells. As described above, differences in the level of expression of the markers of the invention correlate with the cancerous state of cervical cells. Although it is recognized that changes in the levels of expression of certain of the markers of the invention likely result from the cancerous state of cervical cells, it is likewise recognized that changes in the levels of expression of other of the markers of the invention induce, maintain, and promote the cancerous state of those cells. Thus, compounds which inhibit an cervical cancer in a patient will cause the level of expression of one or more of the markers of the invention to change to a level nearer the normal level of expression for that marker (*i.e.* the level of expression for the marker in non-cancerous cervical cells).

This method thus comprises comparing expression of a marker in a first cervical cell sample and maintained in the presence of the test compound and expression of the marker in a second cervical cell sample and maintained in the absence of the test compound. A significantly reduced expression of a marker of the invention in the presence of the test compound is an indication that the test compound inhibits cervical cancer. The cervical cell samples may, for example, be aliquots of a single sample of normal cervical cells obtained from a patient, pooled samples of normal cervical cells obtained from a patient, cells of a normal cervical cell line, aliquots of a single sample of cervical cancer cells obtained from a patient, pooled samples of cervical cancer cells obtained from a patient, cells of an cervical cancer cell line, or the like. In one embodiment, the samples are cervical cancer cells obtained from a patient and a plurality of compounds known to be effective for inhibiting various cervical cancers are tested in order to identify the compound which is likely to best inhibit the cervical cancer in the patient.

This method may likewise be used to assess the efficacy of a therapy for inhibiting cervical cancer in a patient. In this method, the level of expression of one or more markers of the invention in a pair of samples (one subjected to the therapy, the other not subjected to the therapy) is assessed. As with the method of assessing the efficacy of test compounds, if the therapy induces a significantly lower level of expression of a marker of the invention then the therapy is efficacious for inhibiting cervical cancer. As above, if samples from a selected patient are used in this method,

then alternative therapies can be assessed *in vitro* in order to select a therapy most likely to be efficacious for inhibiting cervical cancer in the patient.

As described above, the cancerous state of human cervical cells is correlated with changes in the levels of expression of the markers of the invention. The invention includes a method for assessing the human cervical cell carcinogenic potential of a test compound. This method comprises maintaining separate aliquots of human cervical cells in the presence and absence of the test compound. Expression of a marker of the invention in each of the aliquots is compared. A significantly higher level of expression of a marker of the invention in the aliquot maintained in the presence of the test compound (relative to the aliquot maintained in the absence of the test compound) is an indication that the test compound possesses human cervical cell carcinogenic potential. The relative carcinogenic potentials of various test compounds can be assessed by comparing the degree of enhancement or inhibition of the level of expression of the relevant markers, by comparing the number of markers for which the level of expression is enhanced or inhibited, or by comparing both.

Various aspects of the invention are described in further detail in the following subsections.

#### I. Isolated Nucleic Acid Molecules

One aspect of the invention pertains to isolated nucleic acid molecules, including nucleic acids which encode a marker protein or a portion thereof. Isolated nucleic acids of the invention also include nucleic acid molecules sufficient for use as hybridization probes to identify marker nucleic acid molecules, and fragments of marker nucleic acid molecules, *e.g.*, those suitable for use as PCR primers for the amplification or mutation of marker nucleic acid molecules. As used herein, the term "nucleic acid molecule" is intended to include DNA molecules (*e.g.*, cDNA or genomic DNA) and RNA molecules (*e.g.*, mRNA) and analogs of the DNA or RNA generated using nucleotide analogs. The nucleic acid molecule can be single-stranded or double-stranded, but preferably is double-stranded DNA.

An "isolated" nucleic acid molecule is one which is separated from other nucleic acid molecules which are present in the natural source of the nucleic acid molecule. Preferably, an "isolated" nucleic acid molecule is free of sequences (preferably protein-encoding sequences) which naturally flank the nucleic acid (*i.e.*,

sequences located at the 5' and 3' ends of the nucleic acid) in the genomic DNA of the organism from which the nucleic acid is derived. For example, in various embodiments, the isolated nucleic acid molecule can contain less than about 5 kB, 4 kB, 3 kB, 2 kB, 1 kB, 0.5 kB or 0.1 kB of nucleotide sequences which naturally flank the nucleic acid molecule in genomic DNA of the cell from which the nucleic acid is derived. Moreover, an "isolated" nucleic acid molecule, such as a cDNA molecule, can be substantially free of other cellular material, or culture medium when produced by recombinant techniques, or substantially free of chemical precursors or other chemicals when chemically synthesized.

10                   A nucleic acid molecule of the present invention can be isolated using standard molecular biology techniques and the sequence information in the database records described herein. Using all or a portion of such nucleic acid sequences, nucleic acid molecules of the invention can be isolated using standard hybridization and cloning techniques (*e.g.*, as described in Sambrook *et al.*, ed., *Molecular Cloning: A Laboratory Manual*, 2nd ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 15 1989).

                  A nucleic acid molecule of the invention can be amplified using cDNA, mRNA, or genomic DNA as a template and appropriate oligonucleotide primers according to standard PCR amplification techniques. The nucleic acid so amplified can 20 be cloned into an appropriate vector and characterized by DNA sequence analysis. Furthermore, nucleotides corresponding to all or a portion of a nucleic acid molecule of the invention can be prepared by standard synthetic techniques, *e.g.*, using an automated DNA synthesizer.

                  In another preferred embodiment, an isolated nucleic acid molecule of the invention comprises a nucleic acid molecule which has a nucleotide sequence 25 complementary to the nucleotide sequence of a marker nucleic acid or to the nucleotide sequence of a nucleic acid encoding a marker protein. A nucleic acid molecule which is complementary to a given nucleotide sequence is one which is sufficiently complementary to the given nucleotide sequence that it can hybridize to the given 30 nucleotide sequence thereby forming a stable duplex.

                  Moreover, a nucleic acid molecule of the invention can comprise only a portion of a nucleic acid sequence, wherein the full length nucleic acid sequence comprises a marker nucleic acid or which encodes a marker protein. Such nucleic acids

can be used, for example, as a probe or primer. The probe/primer typically is used as one or more substantially purified oligonucleotides. The oligonucleotide typically comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least about 7, preferably about 15, more preferably about 25, 50, 75, 100, 125, 150,  
5 175, 200, 250, 300, 350, or 400 or more consecutive nucleotides of a nucleic acid of the invention.

Probes based on the sequence of a nucleic acid molecule of the invention can be used to detect transcripts or genomic sequences corresponding to one or more markers of the invention. The probe comprises a label group attached thereto, *e.g.*, a  
10 radioisotope, a fluorescent compound, an enzyme, or an enzyme co-factor. Such probes can be used as part of a diagnostic test kit for identifying cells or tissues which mis-express the protein, such as by measuring levels of a nucleic acid molecule encoding the protein in a sample of cells from a subject, *e.g.*, detecting mRNA levels or determining whether a gene encoding the protein has been mutated or deleted.

15 The invention further encompasses nucleic acid molecules that differ, due to degeneracy of the genetic code, from the nucleotide sequence of nucleic acids encoding a marker protein (*e.g.*, a protein having one of the amino acid sequences set forth in the Sequence Listing), and thus encode the same protein.

It will be appreciated by those skilled in the art that DNA sequence  
20 polymorphisms that lead to changes in the amino acid sequence can exist within a population (*e.g.*, the human population). Such genetic polymorphisms can exist among individuals within a population due to natural allelic variation. An allele is one of a group of genes which occur alternatively at a given genetic locus. In addition, it will be appreciated that DNA polymorphisms that affect RNA expression levels can also exist  
25 that may affect the overall expression level of that gene (*e.g.*, by affecting regulation or degradation).

As used herein, the phrase "allelic variant" refers to a nucleotide sequence which occurs at a given locus or to a polypeptide encoded by the nucleotide sequence.

As used herein, the terms "gene" and "recombinant gene" refer to nucleic  
30 acid molecules comprising an open reading frame encoding a polypeptide corresponding to a marker of the invention. Such natural allelic variations can typically result in 1-5% variance in the nucleotide sequence of a given gene. Alternative alleles can be identified by sequencing the gene of interest in a number of different individuals. This can be

readily carried out by using hybridization probes to identify the same genetic locus in a variety of individuals. Any and all such nucleotide variations and resulting amino acid polymorphisms or variations that are the result of natural allelic variation and that do not alter the functional activity are intended to be within the scope of the invention.

5                   In another embodiment, an isolated nucleic acid molecule of the invention is at least 7, 15, 20, 25, 30, 40, 60, 80, 100, 150, 200, 250, 300, 350, 400, 450, 550, 650, 700, 800, 900, 1000, 1200, 1400, 1600, 1800, 2000, 2200, 2400, 2600, 2800, 3000, 3500, 4000, 4500, or more nucleotides in length and hybridizes under stringent conditions to a marker nucleic acid or to a nucleic acid encoding a marker protein. As  
10                   used herein, the term "hybridizes under stringent conditions" is intended to describe conditions for hybridization and washing under which nucleotide sequences at least 60% (65%, 70%, preferably 75%) identical to each other typically remain hybridized to each other. Such stringent conditions are known to those skilled in the art and can be found in sections 6.3.1-6.3.6 of *Current Protocols in Molecular Biology*, John Wiley & Sons,  
15                   N.Y. (1989). A preferred, non-limiting example of stringent hybridization conditions are hybridization in 6X sodium chloride/sodium citrate (SSC) at about 45°C, followed by one or more washes in 0.2X SSC, 0.1% SDS at 50-65°C.

                  In addition to naturally-occurring allelic variants of a nucleic acid molecule of the invention that can exist in the population, the skilled artisan will further  
20                   appreciate that sequence changes can be introduced by mutation thereby leading to changes in the amino acid sequence of the encoded protein, without altering the biological activity of the protein encoded thereby. For example, one can make nucleotide substitutions leading to amino acid substitutions at "non-essential" amino acid residues. A "non-essential" amino acid residue is a residue that can be altered from  
25                   the wild-type sequence without altering the biological activity, whereas an "essential" amino acid residue is required for biological activity. For example, amino acid residues that are not conserved or only semi-conserved among homologs of various species may be non-essential for activity and thus would be likely targets for alteration.  
                  Alternatively, amino acid residues that are conserved among the homologs of various  
30                   species (*e.g.*, murine and human) may be essential for activity and thus would not be likely targets for alteration.

Accordingly, another aspect of the invention pertains to nucleic acid molecules encoding a variant marker protein that contain changes in amino acid residues that are not essential for activity. Such variant marker proteins differ in amino acid sequence from the naturally-occurring marker proteins, yet retain biological activity. In one embodiment, such a variant marker protein has an amino acid sequence that is at least about 40% identical, 50%, 60%, 70%, 80%, 90%, 95%, or 98% identical to the amino acid sequence of a marker protein.

An isolated nucleic acid molecule encoding a variant marker protein can be created by introducing one or more nucleotide substitutions, additions or deletions into the nucleotide sequence of marker nucleic acids, such that one or more amino acid residue substitutions, additions, or deletions are introduced into the encoded protein. Mutations can be introduced by standard techniques, such as site-directed mutagenesis and PCR-mediated mutagenesis. Preferably, conservative amino acid substitutions are made at one or more predicted non-essential amino acid residues. A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (*e.g.*, lysine, arginine, histidine), acidic side chains (*e.g.*, aspartic acid, glutamic acid), uncharged polar side chains (*e.g.*, glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), non-polar side chains (*e.g.*, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (*e.g.*, threonine, valine, isoleucine) and aromatic side chains (*e.g.*, tyrosine, phenylalanine, tryptophan, histidine). Alternatively, mutations can be introduced randomly along all or part of the coding sequence, such as by saturation mutagenesis, and the resultant mutants can be screened for biological activity to identify mutants that retain activity. Following mutagenesis, the encoded protein can be expressed recombinantly and the activity of the protein can be determined.

The present invention encompasses antisense nucleic acid molecules, *i.e.*, molecules which are complementary to a sense nucleic acid of the invention, *e.g.*, complementary to the coding strand of a double-stranded marker cDNA molecule or complementary to a marker mRNA sequence. Accordingly, an antisense nucleic acid of the invention can hydrogen bond to (*i.e.* anneal with) a sense nucleic acid of the invention. The antisense nucleic acid can be complementary to an entire coding strand,



or to only a portion thereof, *e.g.*, all or part of the protein coding region (or open reading frame). An antisense nucleic acid molecule can also be antisense to all or part of a non-coding region of the coding strand of a nucleotide sequence encoding a marker protein. The non-coding regions ("5' and 3' untranslated regions") are the 5' and 3' sequences  
5 which flank the coding region and are not translated into amino acids.

An antisense oligonucleotide can be, for example, about 5, 10, 15, 20, 25, 30, 35, 40, 45, or 50 or more nucleotides in length. An antisense nucleic acid of the invention can be constructed using chemical synthesis and enzymatic ligation reactions using procedures known in the art. For example, an antisense nucleic acid (*e.g.*, an  
10 antisense oligonucleotide) can be chemically synthesized using naturally occurring nucleotides or variously modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability of the duplex formed between the antisense and sense nucleic acids, *e.g.*, phosphorothioate derivatives and acridine substituted nucleotides can be used. Examples of modified nucleotides which  
15 can be used to generate the antisense nucleic acid include 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxymethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-  
20 methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-  
25 methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine. Alternatively, the antisense nucleic acid can be produced biologically using an expression vector into which a nucleic acid has been sub-cloned in an antisense orientation (*i.e.*, RNA transcribed from the inserted nucleic acid will be of an antisense  
30 orientation to a target nucleic acid of interest, described further in the following subsection).

The antisense nucleic acid molecules of the invention are typically administered to a subject or generated *in situ* such that they hybridize with or bind to cellular mRNA and/or genomic DNA encoding a marker protein to thereby inhibit expression of the marker, *e.g.*, by inhibiting transcription and/or translation. The hybridization can be by conventional nucleotide complementarity to form a stable duplex, or, for example, in the case of an antisense nucleic acid molecule which binds to DNA duplexes, through specific interactions in the major groove of the double helix. Examples of a route of administration of antisense nucleic acid molecules of the invention includes direct injection at a tissue site or infusion of the antisense nucleic acid into an ovary-associated body fluid. Alternatively, antisense nucleic acid molecules can be modified to target selected cells and then administered systemically. For example, for systemic administration, antisense molecules can be modified such that they specifically bind to receptors or antigens expressed on a selected cell surface, *e.g.*, by linking the antisense nucleic acid molecules to peptides or antibodies which bind to cell surface receptors or antigens. The antisense nucleic acid molecules can also be delivered to cells using the vectors described herein. To achieve sufficient intracellular concentrations of the antisense molecules, vector constructs in which the antisense nucleic acid molecule is placed under the control of a strong pol II or pol III promoter are preferred.

An antisense nucleic acid molecule of the invention can be an  $\alpha$ -anomeric nucleic acid molecule. An  $\alpha$ -anomeric nucleic acid molecule forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual  $\alpha$ -units, the strands run parallel to each other (Gaultier *et al.*, 1987, *Nucleic Acids Res.* 15:6625-6641). The antisense nucleic acid molecule can also comprise a 2'-O-methylribonucleotide (Inoue *et al.*, 1987, *Nucleic Acids Res.* 15:6131-6148) or a chimeric RNA-DNA analogue (Inoue *et al.*, 1987, *FEBS Lett.* 215:327-330).

The invention also encompasses ribozymes. Ribozymes are catalytic RNA molecules with ribonuclease activity which are capable of cleaving a single-stranded nucleic acid, such as an mRNA, to which they have a complementary region. Thus, ribozymes (*e.g.*, hammerhead ribozymes as described in Haselhoff and Gerlach, 1988, *Nature* 334:585-591) can be used to catalytically cleave mRNA transcripts to thereby inhibit translation of the protein encoded by the mRNA. A ribozyme having specificity for a nucleic acid molecule encoding a marker protein can be designed based

upon the nucleotide sequence of a cDNA corresponding to the marker. For example, a derivative of a *Tetrahymena* L-19 IVS RNA can be constructed in which the nucleotide sequence of the active site is complementary to the nucleotide sequence to be cleaved (see Cech *et al.* U.S. Patent No. 4,987,071; and Cech *et al.* U.S. Patent No. 5,116,742).

5 Alternatively, an mRNA encoding a polypeptide of the invention can be used to select a catalytic RNA having a specific ribonuclease activity from a pool of RNA molecules (see, *e.g.*, Bartel and Szostak, 1993, *Science* 261:1411-1418).

The invention also encompasses nucleic acid molecules which form triple helical structures. For example, expression of a marker of the invention can be inhibited  
10 by targeting nucleotide sequences complementary to the regulatory region of the gene encoding the marker nucleic acid or protein (*e.g.*, the promoter and/or enhancer) to form triple helical structures that prevent transcription of the gene in target cells. See generally Helene (1991) *Anticancer Drug Des.* 6(6):569-84; Helene (1992) *Ann. N.Y. Acad. Sci.* 660:27-36; and Maher (1992) *Bioassays* 14(12):807-15.

15 In various embodiments, the nucleic acid molecules of the invention can be modified at the base moiety, sugar moiety or phosphate backbone to improve, *e.g.*, the stability, hybridization, or solubility of the molecule. For example, the deoxyribose phosphate backbone of the nucleic acids can be modified to generate peptide nucleic acids (see Hyrup *et al.*, 1996, *Bioorganic & Medicinal Chemistry* 4(1): 5-23). As used  
20 herein, the terms "peptide nucleic acids" or "PNAs" refer to nucleic acid mimics, *e.g.*, DNA mimics, in which the deoxyribose phosphate backbone is replaced by a pseudopeptide backbone and only the four natural nucleobases are retained. The neutral backbone of PNAs has been shown to allow for specific hybridization to DNA and RNA under conditions of low ionic strength. The synthesis of PNA oligomers can be  
25 performed using standard solid phase peptide synthesis protocols as described in Hyrup *et al.* (1996), *supra*; Perry-O'Keefe *et al.* (1996) *Proc. Natl. Acad. Sci. USA* 93:14670-675.

PNAs can be used in therapeutic and diagnostic applications. For example, PNAs can be used as antisense or antigene agents for sequence-specific  
30 modulation of gene expression by, *e.g.*, inducing transcription or translation arrest or inhibiting replication. PNAs can also be used, *e.g.*, in the analysis of single base pair mutations in a gene by, *e.g.*, PNA directed PCR clamping; as artificial restriction enzymes when used in combination with other enzymes, *e.g.*, S1 nucleases (Hyrup

(1996), *supra*; or as probes or primers for DNA sequence and hybridization (Hyrup, 1996, *supra*; Perry-O'Keefe *et al.*, 1996, *Proc. Natl. Acad. Sci. USA* 93:14670-675).

In another embodiment, PNAs can be modified, *e.g.*, to enhance their stability or cellular uptake, by attaching lipophilic or other helper groups to PNA, by the formation of PNA-DNA chimeras, or by the use of liposomes or other techniques of drug delivery known in the art. For example, PNA-DNA chimeras can be generated which can combine the advantageous properties of PNA and DNA. Such chimeras allow DNA recognition enzymes, *e.g.*, RNase H and DNA polymerases, to interact with the DNA portion while the PNA portion would provide high binding affinity and specificity. PNA-DNA chimeras can be linked using linkers of appropriate lengths selected in terms of base stacking, number of bonds between the nucleobases, and orientation (Hyrup, 1996, *supra*). The synthesis of PNA-DNA chimeras can be performed as described in Hyrup (1996), *supra*, and Finn *et al.* (1996) *Nucleic Acids Res.* 24(17):3357-63. For example, a DNA chain can be synthesized on a solid support using standard phosphoramidite coupling chemistry and modified nucleoside analogs. Compounds such as 5'-(4-methoxytrityl)amino-5'-deoxy-thymidine phosphoramidite can be used as a link between the PNA and the 5' end of DNA (Mag *et al.*, 1989, *Nucleic Acids Res.* 17:5973-88). PNA monomers are then coupled in a step-wise manner to produce a chimeric molecule with a 5' PNA segment and a 3' DNA segment (Finn *et al.*, 1996, *Nucleic Acids Res.* 24(17):3357-63). Alternatively, chimeric molecules can be synthesized with a 5' DNA segment and a 3' PNA segment (Peterser *et al.*, 1975, *Bioorganic Med. Chem. Lett.* 5:1119-1124).

In other embodiments, the oligonucleotide can include other appended groups such as peptides (*e.g.*, for targeting host cell receptors *in vivo*), or agents facilitating transport across the cell membrane (see, *e.g.*, Letsinger *et al.*, 1989, *Proc. Natl. Acad. Sci. USA* 86:6553-6556; Lemaitre *et al.*, 1987, *Proc. Natl. Acad. Sci. USA* 84:648-652; PCT Publication No. WO 88/09810) or the blood-brain barrier (see, *e.g.*, PCT Publication No. WO 89/10134). In addition, oligonucleotides can be modified with hybridization-triggered cleavage agents (see, *e.g.*, Krol *et al.*, 1988, *Bio/Techniques* 6:958-976) or intercalating agents (see, *e.g.*, Zon, 1988, *Pharm. Res.* 5:539-549). To this end, the oligonucleotide can be conjugated to another molecule, *e.g.*, a peptide, hybridization triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent, etc.

The invention also includes molecular beacon nucleic acids having at least one region which is complementary to a nucleic acid of the invention, such that the molecular beacon is useful for quantitating the presence of the nucleic acid of the invention in a sample. A "molecular beacon" nucleic acid is a nucleic acid comprising a pair of complementary regions and having a fluorophore and a fluorescent quencher associated therewith. The fluorophore and quencher are associated with different portions of the nucleic acid in such an orientation that when the complementary regions are annealed with one another, fluorescence of the fluorophore is quenched by the quencher. When the complementary regions of the nucleic acid are not annealed with one another, fluorescence of the fluorophore is quenched to a lesser degree. Molecular beacon nucleic acids are described, for example, in U.S. Patent 5,876,930.

## II. Isolated Proteins and Antibodies

One aspect of the invention pertains to isolated marker proteins and biologically active portions thereof, as well as polypeptide fragments suitable for use as immunogens to raise antibodies directed against a marker protein or a fragment thereof. In one embodiment, the native marker protein can be isolated from cells or tissue sources by an appropriate purification scheme using standard protein purification techniques. In another embodiment, a protein or peptide comprising the whole or a segment of the marker protein is produced by recombinant DNA techniques. Alternative to recombinant expression, such protein or peptide can be synthesized chemically using standard peptide synthesis techniques.

An "isolated" or "purified" protein or biologically active portion thereof is substantially free of cellular material or other contaminating proteins from the cell or tissue source from which the protein is derived, or substantially free of chemical precursors or other chemicals when chemically synthesized. The language "substantially free of cellular material" includes preparations of protein in which the protein is separated from cellular components of the cells from which it is isolated or recombinantly produced. Thus, protein that is substantially free of cellular material includes preparations of protein having less than about 30%, 20%, 10%, or 5% (by dry weight) of heterologous protein (also referred to herein as a "contaminating protein"). When the protein or biologically active portion thereof is recombinantly produced, it is also preferably substantially free of culture medium, *i.e.*, culture medium represents less

than about 20%, 10%, or 5% of the volume of the protein preparation. When the protein is produced by chemical synthesis, it is preferably substantially free of chemical precursors or other chemicals, *i.e.*, it is separated from chemical precursors or other chemicals which are involved in the synthesis of the protein. Accordingly such  
5 preparations of the protein have less than about 30%, 20%, 10%, 5% (by dry weight) of chemical precursors or compounds other than the polypeptide of interest.

Biologically active portions of a marker protein include polypeptides comprising amino acid sequences sufficiently identical to or derived from the amino acid sequence of the marker protein, which include fewer amino acids than the full  
10 length protein, and exhibit at least one activity of the corresponding full-length protein. Typically, biologically active portions comprise a domain or motif with at least one activity of the corresponding full-length protein. A biologically active portion of a marker protein of the invention can be a polypeptide which is, for example, 10, 25, 50, 100 or more amino acids in length. Moreover, other biologically active portions, in  
15 which other regions of the marker protein are deleted, can be prepared by recombinant techniques and evaluated for one or more of the functional activities of the native form of the marker protein.

Preferred marker proteins are encoded by nucleotide sequences comprising the sequence of any of the sequences set forth in the Sequence Listing.  
20 Other useful proteins are substantially identical (*e.g.*, at least about 40%, preferably 50%, 60%, 70%, 80%, 90%, 95%, or 99%) to one of these sequences and retain the functional activity of the corresponding naturally-occurring marker protein yet differ in amino acid sequence due to natural allelic variation or mutagenesis.

To determine the percent identity of two amino acid sequences or of two  
25 nucleic acids, the sequences are aligned for optimal comparison purposes (*e.g.*, gaps can be introduced in the sequence of a first amino acid or nucleic acid sequence for optimal alignment with a second amino or nucleic acid sequence). The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid  
30 residue or nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences (*i.e.*, %

identity = # of identical positions/total # of positions (*e.g.*, overlapping positions) x100).  
In one embodiment the two sequences are the same length.

The determination of percent identity between two sequences can be accomplished using a mathematical algorithm. A preferred, non-limiting example of a  
5 mathematical algorithm utilized for the comparison of two sequences is the algorithm of Karlin and Altschul (1990) *Proc. Natl. Acad. Sci. USA* 87:2264-2268, modified as in Karlin and Altschul (1993) *Proc. Natl. Acad. Sci. USA* 90:5873-5877. Such an algorithm is incorporated into the BLASTN and BLASTX programs of Altschul, *et al.* (1990) *J. Mol. Biol.* 215:403-410. BLAST nucleotide searches can be performed with  
10 the BLASTN program, score = 100, wordlength = 12 to obtain nucleotide sequences homologous to a nucleic acid molecules of the invention. BLAST protein searches can be performed with the BLASTP program, score = 50, wordlength = 3 to obtain amino acid sequences homologous to a protein molecules of the invention. To obtain gapped alignments for comparison purposes, a newer version of the BLAST algorithm called  
15 Gapped BLAST can be utilized as described in Altschul *et al.* (1997) *Nucleic Acids Res.* 25:3389-3402, which is able to perform gapped local alignments for the programs BLASTN, BLASTP and BLASTX. Alternatively, PSI-Blast can be used to perform an iterated search which detects distant relationships between molecules. When utilizing BLAST, Gapped BLAST, and PSI-Blast programs, the default parameters of the  
20 respective programs (*e.g.*, BLASTX and BLASTN) can be used. See <http://www.ncbi.nlm.nih.gov>. Another preferred, non-limiting example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller, (1988) *CABIOS* 4:11-17. Such an algorithm is incorporated into the ALIGN program (version 2.0) which is part of the GCG sequence alignment software  
25 package. When utilizing the ALIGN program for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 can be used. Yet another useful algorithm for identifying regions of local sequence similarity and alignment is the FASTA algorithm as described in Pearson and Lipman (1988) *Proc. Natl. Acad. Sci. USA* 85:2444-2448. When using the FASTA algorithm for  
30 comparing nucleotide or amino acid sequences, a PAM120 weight residue table can, for example, be used with a *k*-tuple value of 2.

The percent identity between two sequences can be determined using techniques similar to those described above, with or without allowing gaps. In calculating percent identity, only exact matches are counted.

The invention also provides chimeric or fusion proteins comprising a marker protein or a segment thereof. As used herein, a "chimeric protein" or "fusion protein" comprises all or part (preferably a biologically active part) of a marker protein operably linked to a heterologous polypeptide (*i.e.*, a polypeptide other than the marker protein). Within the fusion protein, the term "operably linked" is intended to indicate that the marker protein or segment thereof and the heterologous polypeptide are fused in-frame to each other. The heterologous polypeptide can be fused to the amino-terminus or the carboxyl-terminus of the marker protein or segment.

One useful fusion protein is a GST fusion protein in which a marker protein or segment is fused to the carboxyl terminus of GST sequences. Such fusion proteins can facilitate the purification of a recombinant polypeptide of the invention.

In another embodiment, the fusion protein contains a heterologous signal sequence at its amino terminus. For example, the native signal sequence of a marker protein can be removed and replaced with a signal sequence from another protein. For example, the gp67 secretory sequence of the baculovirus envelope protein can be used as a heterologous signal sequence (Ausubel *et al.*, ed., *Current Protocols in Molecular Biology*, John Wiley & Sons, NY, 1992). Other examples of eukaryotic heterologous signal sequences include the secretory sequences of melittin and human placental alkaline phosphatase (Stratagene; La Jolla, California). In yet another example, useful prokaryotic heterologous signal sequences include the phoA secretory signal (Sambrook *et al.*, *supra*) and the protein A secretory signal (Pharmacia Biotech; Piscataway, New Jersey).

In yet another embodiment, the fusion protein is an immunoglobulin fusion protein in which all or part of a marker protein is fused to sequences derived from a member of the immunoglobulin protein family. The immunoglobulin fusion proteins of the invention can be incorporated into pharmaceutical compositions and administered to a subject to inhibit an interaction between a ligand (soluble or membrane-bound) and a protein on the surface of a cell (receptor), to thereby suppress signal transduction *in vivo*. The immunoglobulin fusion protein can be used to affect the bioavailability of a cognate ligand of a marker protein. Inhibition of ligand/receptor interaction can be



useful therapeutically, both for treating proliferative and differentiative disorders and for modulating (*e.g.* promoting or inhibiting) cell survival. Moreover, the immunoglobulin fusion proteins of the invention can be used as immunogens to produce antibodies directed against a marker protein in a subject, to purify ligands and in screening assays  
5 to identify molecules which inhibit the interaction of the marker protein with ligands.

Chimeric and fusion proteins of the invention can be produced by standard recombinant DNA techniques. In another embodiment, the fusion gene can be synthesized by conventional techniques including automated DNA synthesizers. Alternatively, PCR amplification of gene fragments can be carried out using anchor  
10 primers which give rise to complementary overhangs between two consecutive gene fragments which can subsequently be annealed and re-amplified to generate a chimeric gene sequence (see, *e.g.*, Ausubel *et al.*, *supra*). Moreover, many expression vectors are commercially available that already encode a fusion moiety (*e.g.*, a GST polypeptide). A nucleic acid encoding a polypeptide of the invention can be cloned into such an  
15 expression vector such that the fusion moiety is linked in-frame to the polypeptide of the invention.

A signal sequence can be used to facilitate secretion and isolation of marker proteins. Signal sequences are typically characterized by a core of hydrophobic amino acids which are generally cleaved from the mature protein during secretion in one  
20 or more cleavage events. Such signal peptides contain processing sites that allow cleavage of the signal sequence from the mature proteins as they pass through the secretory pathway. Thus, the invention pertains to marker proteins, fusion proteins or segments thereof having a signal sequence, as well as to such proteins from which the signal sequence has been proteolytically cleaved (*i.e.*, the cleavage products). In one  
25 embodiment, a nucleic acid sequence encoding a signal sequence can be operably linked in an expression vector to a protein of interest, such as a marker protein or a segment thereof. The signal sequence directs secretion of the protein, such as from a eukaryotic host into which the expression vector is transformed, and the signal sequence is subsequently or concurrently cleaved. The protein can then be readily purified from the  
30 extracellular medium by art recognized methods. Alternatively, the signal sequence can be linked to the protein of interest using a sequence which facilitates purification, such as with a GST domain.

The present invention also pertains to variants of the marker proteins.

Such variants have an altered amino acid sequence which can function as either agonists (mimetics) or as antagonists. Variants can be generated by mutagenesis, *e.g.*, discrete point mutation or truncation. An agonist can retain substantially the same, or a subset, of the biological activities of the naturally occurring form of the protein. An antagonist of a protein can inhibit one or more of the activities of the naturally occurring form of the protein by, for example, competitively binding to a downstream or upstream member of a cellular signaling cascade which includes the protein of interest. Thus, specific biological effects can be elicited by treatment with a variant of limited function.

10 Treatment of a subject with a variant having a subset of the biological activities of the naturally occurring form of the protein can have fewer side effects in a subject relative to treatment with the naturally occurring form of the protein.

Variants of a marker protein which function as either agonists (mimetics) or as antagonists can be identified by screening combinatorial libraries of mutants, *e.g.*, truncation mutants, of the protein of the invention for agonist or antagonist activity. In one embodiment, a variegated library of variants is generated by combinatorial mutagenesis at the nucleic acid level and is encoded by a variegated gene library. A variegated library of variants can be produced by, for example, enzymatically ligating a mixture of synthetic oligonucleotides into gene sequences such that a degenerate set of potential protein sequences is expressible as individual polypeptides, or alternatively, as a set of larger fusion proteins (*e.g.*, for phage display). There are a variety of methods which can be used to produce libraries of potential variants of the marker proteins from a degenerate oligonucleotide sequence. Methods for synthesizing degenerate oligonucleotides are known in the art (see, *e.g.*, Narang, 1983, *Tetrahedron* 39:3; Itakura *et al.*, 1984, *Annu. Rev. Biochem.* 53:323; Itakura *et al.*, 1984, *Science* 198:1056; Ike *et al.*, 1983 *Nucleic Acid Res.* 11:477).

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In addition, libraries of segments of a marker protein can be used to generate a variegated population of polypeptides for screening and subsequent selection of variant marker proteins or segments thereof. For example, a library of coding sequence fragments can be generated by treating a double stranded PCR fragment of the coding sequence of interest with a nuclease under conditions wherein nicking occurs only about once per molecule, denaturing the double stranded DNA, renaturing the DNA to form double stranded DNA which can include sense/antisense pairs from different

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nicked products, removing single stranded portions from reformed duplexes by treatment with S1 nuclease, and ligating the resulting fragment library into an expression vector. By this method, an expression library can be derived which encodes amino terminal and internal fragments of various sizes of the protein of interest.

5               Several techniques are known in the art for screening gene products of combinatorial libraries made by point mutations or truncation, and for screening cDNA libraries for gene products having a selected property. The most widely used techniques, which are amenable to high through-put analysis, for screening large gene libraries typically include cloning the gene library into replicable expression vectors,  
10 transforming appropriate cells with the resulting library of vectors, and expressing the combinatorial genes under conditions in which detection of a desired activity facilitates isolation of the vector encoding the gene whose product was detected. Recursive ensemble mutagenesis (REM), a technique which enhances the frequency of functional mutants in the libraries, can be used in combination with the screening assays to identify  
15 variants of a protein of the invention (Arkin and Yourvan, 1992, *Proc. Natl. Acad. Sci. USA* 89:7811-7815; Delgrave *et al.*, 1993, *Protein Engineering* 6(3):327- 331).

Another aspect of the invention pertains to antibodies directed against a protein of the invention. In preferred embodiments, the antibodies specifically bind a marker protein or a fragment thereof. The terms "antibody" and "antibodies" as used  
20 interchangeably herein refer to immunoglobulin molecules as well as fragments and derivatives thereof that comprise an immunologically active portion of an immunoglobulin molecule, (*i.e.*, such a portion contains an antigen binding site which specifically binds an antigen, such as a marker protein, *e.g.*, an epitope of a marker protein). An antibody which specifically binds to a protein of the invention is an  
25 antibody which binds the protein, but does not substantially bind other molecules in a sample, *e.g.*, a biological sample, which naturally contains the protein. Examples of an immunologically active portion of an immunoglobulin molecule include, but are not limited to, single-chain antibodies (scAb), F(ab) and F(ab')<sub>2</sub> fragments.

An isolated protein of the invention or a fragment thereof can be used as  
30 an immunogen to generate antibodies. The full-length protein can be used or, alternatively, the invention provides antigenic peptide fragments for use as immunogens. The antigenic peptide of a protein of the invention comprises at least 8 (preferably 10, 15, 20, or 30 or more) amino acid residues of the amino acid sequence of one of the

proteins of the invention, and encompasses at least one epitope of the protein such that an antibody raised against the peptide forms a specific immune complex with the protein. Preferred epitopes encompassed by the antigenic peptide are regions that are located on the surface of the protein, *e.g.*, hydrophilic regions. Hydrophobicity sequence analysis, hydrophilicity sequence analysis, or similar analyses can be used to identify hydrophilic regions. In preferred embodiments, an isolated marker protein or fragment thereof is used as an immunogen.

An immunogen typically is used to prepare antibodies by immunizing a suitable (*i.e.* immunocompetent) subject such as a rabbit, goat, mouse, or other mammal or vertebrate. An appropriate immunogenic preparation can contain, for example, recombinantly-expressed or chemically-synthesized protein or peptide. The preparation can further include an adjuvant, such as Freund's complete or incomplete adjuvant, or a similar immunostimulatory agent. Preferred immunogen compositions are those that contain no other human proteins such as, for example, immunogen compositions made using a non-human host cell for recombinant expression of a protein of the invention. In such a manner, the resulting antibody compositions have reduced or no binding of human proteins other than a protein of the invention.

The invention provides polyclonal and monoclonal antibodies. The term "monoclonal antibody" or "monoclonal antibody composition", as used herein, refers to a population of antibody molecules that contain only one species of an antigen binding site capable of immunoreacting with a particular epitope. Preferred polyclonal and monoclonal antibody compositions are ones that have been selected for antibodies directed against a protein of the invention. Particularly preferred polyclonal and monoclonal antibody preparations are ones that contain only antibodies directed against a marker protein or fragment thereof.

Polyclonal antibodies can be prepared by immunizing a suitable subject with a protein of the invention as an immunogen. The antibody titer in the immunized subject can be monitored over time by standard techniques, such as with an enzyme linked immunosorbent assay (ELISA) using immobilized polypeptide. At an appropriate time after immunization, *e.g.*, when the specific antibody titers are highest, antibody-producing cells can be obtained from the subject and used to prepare monoclonal antibodies (mAb) by standard techniques, such as the hybridoma technique originally described by Kohler and Milstein (1975) *Nature* 256:495-497, the human B cell

hybridoma technique (see Kozbor *et al.*, 1983, *Immunol. Today* 4:72), the EBV-hybridoma technique (see Cole *et al.*, pp. 77-96 In *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, Inc., 1985) or trioma techniques. The technology for producing hybridomas is well known (see generally *Current Protocols in Immunology*, Coligan *et al.* ed., John Wiley & Sons, New York, 1994). Hybridoma cells producing a monoclonal antibody of the invention are detected by screening the hybridoma culture supernatants for antibodies that bind the polypeptide of interest, *e.g.*, using a standard ELISA assay.

Alternative to preparing monoclonal antibody-secreting hybridomas, a monoclonal antibody directed against a protein of the invention can be identified and isolated by screening a recombinant combinatorial immunoglobulin library (*e.g.*, an antibody phage display library) with the polypeptide of interest. Kits for generating and screening phage display libraries are commercially available (*e.g.*, the Pharmacia *Recombinant Phage Antibody System*, Catalog No. 27-9400-01; and the Stratagene *SurfZAP Phage Display Kit*, Catalog No. 240612). Additionally, examples of methods and reagents particularly amenable for use in generating and screening antibody display library can be found in, for example, U.S. Patent No. 5,223,409; PCT Publication No. WO 92/18619; PCT Publication No. WO 91/17271; PCT Publication No. WO 92/20791; PCT Publication No. WO 92/15679; PCT Publication No. WO 93/01288; PCT Publication No. WO 92/01047; PCT Publication No. WO 92/09690; PCT Publication No. WO 90/02809; Fuchs *et al.* (1991) *Bio/Technology* 9:1370-1372; Hay *et al.* (1992) *Hum. Antibod. Hybridomas* 3:81-85; Huse *et al.* (1989) *Science* 246:1275- 1281; Griffiths *et al.* (1993) *EMBO J.* 12:725-734.

The invention also provides recombinant antibodies that specifically bind a protein of the invention. In preferred embodiments, the recombinant antibodies specifically binds a marker protein or fragment thereof. Recombinant antibodies include, but are not limited to, chimeric and humanized monoclonal antibodies, comprising both human and non-human portions, single-chain antibodies and multi-specific antibodies. A chimeric antibody is a molecule in which different portions are derived from different animal species, such as those having a variable region derived from a murine mAb and a human immunoglobulin constant region. (See, *e.g.*, Cabilly *et al.*, U.S. Patent No. 4,816,567; and Boss *et al.*, U.S. Patent No. 4,816,397, which are incorporated herein by reference in their entirety.) Single-chain antibodies have an

antigen binding site and consist of a single polypeptide. They can be produced by techniques known in the art, for example using methods described in Ladner *et al.* U.S. Pat. No. 4,946,778 (which is incorporated herein by reference in its entirety); Bird *et al.*, (1988) *Science* 242:423-426; Whitlow *et al.*, (1991) *Methods in Enzymology* 2:1-9; 5 Whitlow *et al.*, (1991) *Methods in Enzymology* 2:97-105; and Huston *et al.*, (1991) *Methods in Enzymology Molecular Design and Modeling: Concepts and Applications* 203:46-88. Multi-specific antibodies are antibody molecules having at least two antigen-binding sites that specifically bind different antigens. Such molecules can be produced by techniques known in the art, for example using methods described in Segal, 10 U.S. Patent No. 4,676,980 (the disclosure of which is incorporated herein by reference in its entirety); Holliger *et al.*, (1993) *Proc. Natl. Acad. Sci. USA* 90:6444-6448; Whitlow *et al.*, (1994) *Protein Eng.* 7:1017-1026 and U.S. Pat. No. 6,121,424.

Humanized antibodies are antibody molecules from non-human species having one or more complementarity determining regions (CDRs) from the non-human 15 species and a framework region from a human immunoglobulin molecule. (See, *e.g.*, Queen, U.S. Patent No. 5,585,089, which is incorporated herein by reference in its entirety.) Humanized monoclonal antibodies can be produced by recombinant DNA techniques known in the art, for example using methods described in PCT Publication No. WO 87/02671; European Patent Application 184,187; European Patent Application 20 171,496; European Patent Application 173,494; PCT Publication No. WO 86/01533; U.S. Patent No. 4,816,567; European Patent Application 125,023; Better *et al.* (1988) *Science* 240:1041-1043; Liu *et al.* (1987) *Proc. Natl. Acad. Sci. USA* 84:3439-3443; Liu *et al.* (1987) *J. Immunol.* 139:3521- 3526; Sun *et al.* (1987) *Proc. Natl. Acad. Sci. USA* 84:214-218; Nishimura *et al.* (1987) *Cancer Res.* 47:999-1005; Wood *et al.* (1985) 25 *Nature* 314:446-449; and Shaw *et al.* (1988) *J. Natl. Cancer Inst.* 80:1553-1559; Morrison (1985) *Science* 229:1202-1207; Oi *et al.* (1986) *Bio/Techniques* 4:214; U.S. Patent 5,225,539; Jones *et al.* (1986) *Nature* 321:552-525; Verhoeyan *et al.* (1988) *Science* 239:1534; and Beidler *et al.* (1988) *J. Immunol.* 141:4053-4060.

More particularly, humanized antibodies can be produced, for example, 30 using transgenic mice which are incapable of expressing endogenous immunoglobulin heavy and light chains genes, but which can express human heavy and light chain genes. The transgenic mice are immunized in the normal fashion with a selected antigen, *e.g.*, all or a portion of a polypeptide corresponding to a marker of the invention. Monoclonal

antibodies directed against the antigen can be obtained using conventional hybridoma technology. The human immunoglobulin transgenes harbored by the transgenic mice rearrange during B cell differentiation, and subsequently undergo class switching and somatic mutation. Thus, using such a technique, it is possible to produce therapeutically useful IgG, IgA and IgE antibodies. For an overview of this technology for producing human antibodies, see Lonberg and Huszar (1995) *Int. Rev. Immunol.* 13:65-93). For a detailed discussion of this technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, see, e.g., U.S. Patent 5,625,126; U.S. Patent 5,633,425; U.S. Patent 5,569,825; U.S. Patent 5,661,016; and U.S. Patent 5,545,806. In addition, companies such as Abgenix, Inc. (Freemont, CA), can be engaged to provide human antibodies directed against a selected antigen using technology similar to that described above.

Completely human antibodies which recognize a selected epitope can be generated using a technique referred to as "guided selection." In this approach a selected non-human monoclonal antibody, e.g., a murine antibody, is used to guide the selection of a completely human antibody recognizing the same epitope (Jespers *et al.*, 1994, *Bio/technology* 12:899-903).

The antibodies of the invention can be isolated after production (e.g., from the blood or serum of the subject) or synthesis and further purified by well-known techniques. For example, IgG antibodies can be purified using protein A chromatography. Antibodies specific for a protein of the invention can be selected or (e.g., partially purified) or purified by, e.g., affinity chromatography. For example, a recombinantly expressed and purified (or partially purified) protein of the invention is produced as described herein, and covalently or non-covalently coupled to a solid support such as, for example, a chromatography column. The column can then be used to affinity purify antibodies specific for the proteins of the invention from a sample containing antibodies directed against a large number of different epitopes, thereby generating a substantially purified antibody composition, *i.e.*, one that is substantially free of contaminating antibodies. By a substantially purified antibody composition is meant, in this context, that the antibody sample contains at most only 30% (by dry weight) of contaminating antibodies directed against epitopes other than those of the desired protein of the invention, and preferably at most 20%, yet more preferably at most 10%, and most preferably at most 5% (by dry weight) of the sample is

contaminating antibodies. A purified antibody composition means that at least 99% of the antibodies in the composition are directed against the desired protein of the invention.

In a preferred embodiment, the substantially purified antibodies of the invention may specifically bind to a signal peptide, a secreted sequence, an extracellular domain, a transmembrane or a cytoplasmic domain or cytoplasmic membrane of a protein of the invention. In a particularly preferred embodiment, the substantially purified antibodies of the invention specifically bind to a secreted sequence or an extracellular domain of the amino acid sequences of a protein of the invention. In a more preferred embodiment, the substantially purified antibodies of the invention specifically bind to a secreted sequence or an extracellular domain of the amino acid sequences of a marker protein.

An antibody directed against a protein of the invention can be used to isolate the protein by standard techniques, such as affinity chromatography or immunoprecipitation. Moreover, such an antibody can be used to detect the marker protein or fragment thereof (*e.g.*, in a cellular lysate or cell supernatant) in order to evaluate the level and pattern of expression of the marker. The antibodies can also be used diagnostically to monitor protein levels in tissues or body fluids (*e.g.* in a cervical-associated body fluid) as part of a clinical testing procedure, *e.g.*, to, for example, determine the efficacy of a given treatment regimen. Detection can be facilitated by the use of an antibody derivative, which comprises an antibody of the invention coupled to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase,  $\beta$ -galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin, and examples of suitable radioactive material include  $^{125}\text{I}$ ,  $^{131}\text{I}$ ,  $^{35}\text{S}$  or  $^3\text{H}$ .



Antibodies of the invention may also be used as therapeutic agents in treating cancers. In a preferred embodiment, completely human antibodies of the invention are used for therapeutic treatment of human cancer patients, particularly those having an cervical cancer. In another preferred embodiment, antibodies that bind

5 specifically to a marker protein or fragment thereof are used for therapeutic treatment. Further, such therapeutic antibody may be an antibody derivative or immunotoxin comprising an antibody conjugated to a therapeutic moiety such as a cytotoxin, a therapeutic agent or a radioactive metal ion. A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include taxol, cytochalasin B, gramicidin D,

10 ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (*e.g.*, methotrexate,

15 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (*e.g.*, mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (*e.g.*, daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (*e.g.*,

20 dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (*e.g.*, vincristine and vinblastine).

The conjugated antibodies of the invention can be used for modifying a given biological response, for the drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or

25 polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as ribosome-inhibiting protein (see Better et al., U.S. Patent No. 6,146,631, the disclosure of which is incorporated herein in its entirety), abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a protein such as tumor necrosis factor, .alpha.-interferon, .beta.-interferon, nerve growth factor, platelet derived growth factor,

30 tissue plasminogen activator; or, biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophase colony stimulating factor ("GM-CSF"), granulocyte colony stimulating factor ("G-CSF"), or other growth factors.

Techniques for conjugating such therapeutic moiety to antibodies are well known, see, *e.g.*, Arnon et al., "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in *Monoclonal Antibodies And Cancer Therapy*, Reisfeld et al. (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom et al., "Antibodies For Drug  
5 Delivery", in *Controlled Drug Delivery* (2nd Ed.), Robinson et al. (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in *Monoclonal Antibodies '84: Biological And Clinical Applications*, Pinchera et al. (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in  
10 *Monoclonal Antibodies For Cancer Detection And Therapy*, Baldwin et al. (eds.), pp. 303-16 (Academic Press 1985), and Thorpe et al., "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", *Immunol. Rev.*, 62:119-58 (1982).

Accordingly, in one aspect, the invention provides substantially purified antibodies, antibody fragments and derivatives, all of which specifically bind to a  
15 protein of the invention and preferably, a marker protein. In various embodiments, the substantially purified antibodies of the invention, or fragments or derivatives thereof, can be human, non-human, chimeric and/or humanized antibodies. In another aspect, the invention provides non-human antibodies, antibody fragments and derivatives, all of which specifically bind to a protein of the invention and preferably, a marker protein.  
20 Such non-human antibodies can be goat, mouse, sheep, horse, chicken, rabbit, or rat antibodies. Alternatively, the non-human antibodies of the invention can be chimeric and/or humanized antibodies. In addition, the non-human antibodies of the invention can be polyclonal antibodies or monoclonal antibodies. In still a further aspect, the invention provides monoclonal antibodies, antibody fragments and derivatives, all of  
25 which specifically bind to a protein of the invention and preferably, a marker protein. The monoclonal antibodies can be human, humanized, chimeric and/or non-human antibodies.

The invention also provides a kit containing an antibody of the invention conjugated to a detectable substance, and instructions for use. Still another aspect of the  
30 invention is a pharmaceutical composition comprising an antibody of the invention. In one embodiment, the pharmaceutical composition comprises an antibody of the invention and a pharmaceutically acceptable carrier.

### III. Recombinant Expression Vectors and Host Cells

Another aspect of the invention pertains to vectors, preferably expression vectors, containing a nucleic acid encoding a marker protein (or a portion of such a protein). As used herein, the term "vector" refers to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a "plasmid", which refers to a circular double stranded DNA loop into which additional DNA segments can be ligated. Another type of vector is a viral vector, wherein additional DNA segments can be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (*e.g.*, bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (*e.g.*, non-episomal mammalian vectors) are integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors, namely expression vectors, are capable of directing the expression of genes to which they are operably linked. In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids (vectors). However, the invention is intended to include such other forms of expression vectors, such as viral vectors (*e.g.*, replication defective retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions.

The recombinant expression vectors of the invention comprise a nucleic acid of the invention in a form suitable for expression of the nucleic acid in a host cell. This means that the recombinant expression vectors include one or more regulatory sequences, selected on the basis of the host cells to be used for expression, which is operably linked to the nucleic acid sequence to be expressed. Within a recombinant expression vector, "operably linked" is intended to mean that the nucleotide sequence of interest is linked to the regulatory sequence(s) in a manner which allows for expression of the nucleotide sequence (*e.g.*, in an *in vitro* transcription/translation system or in a host cell when the vector is introduced into the host cell). The term "regulatory sequence" is intended to include promoters, enhancers and other expression control elements (*e.g.*, polyadenylation signals). Such regulatory sequences are described, for example, in Goeddel, *Methods in Enzymology: Gene Expression Technology* vol.185, Academic Press, San Diego, CA (1991). Regulatory sequences include those which direct constitutive expression of a nucleotide sequence in many types of host cell and

those which direct expression of the nucleotide sequence only in certain host cells (*e.g.*, tissue-specific regulatory sequences). It will be appreciated by those skilled in the art that the design of the expression vector can depend on such factors as the choice of the host cell to be transformed, the level of expression of protein desired, and the like. The expression vectors of the invention can be introduced into host cells to thereby produce proteins or peptides, including fusion proteins or peptides, encoded by nucleic acids as described herein.

The recombinant expression vectors of the invention can be designed for expression of a marker protein or a segment thereof in prokaryotic (*e.g.*, *E. coli*) or eukaryotic cells (*e.g.*, insect cells {using baculovirus expression vectors}, yeast cells or mammalian cells). Suitable host cells are discussed further in Goeddel, *supra*. Alternatively, the recombinant expression vector can be transcribed and translated *in vitro*, for example using T7 promoter regulatory sequences and T7 polymerase.

Expression of proteins in prokaryotes is most often carried out in *E. coli* with vectors containing constitutive or inducible promoters directing the expression of either fusion or non-fusion proteins. Fusion vectors add a number of amino acids to a protein encoded therein, usually to the amino terminus of the recombinant protein. Such fusion vectors typically serve three purposes: 1) to increase expression of recombinant protein; 2) to increase the solubility of the recombinant protein; and 3) to aid in the purification of the recombinant protein by acting as a ligand in affinity purification. Often, in fusion expression vectors, a proteolytic cleavage site is introduced at the junction of the fusion moiety and the recombinant protein to enable separation of the recombinant protein from the fusion moiety subsequent to purification of the fusion protein. Such enzymes, and their cognate recognition sequences, include Factor Xa, thrombin and enterokinase. Typical fusion expression vectors include pGEX (Pharmacia Biotech Inc; Smith and Johnson, 1988, *Gene* 67:31-40), pMAL (New England Biolabs, Beverly, MA) and pRIT5 (Pharmacia, Piscataway, NJ) which fuse glutathione S-transferase (GST), maltose E binding protein, or protein A, respectively, to the target recombinant protein.

Examples of suitable inducible non-fusion *E. coli* expression vectors include pTrc (Amann *et al.*, 1988, *Gene* 69:301-315) and pET 11d (Studier *et al.*, p. 60-89, In *Gene Expression Technology: Methods in Enzymology* vol.185, Academic Press, San Diego, CA, 1991). Target gene expression from the pTrc vector relies on host RNA

polymerase transcription from a hybrid trp-lac fusion promoter. Target gene expression from the pET 11d vector relies on transcription from a T7 gn10-lac fusion promoter mediated by a co-expressed viral RNA polymerase (T7 gn1). This viral polymerase is supplied by host strains BL21(DE3) or HMS174(DE3) from a resident prophage  
5 harboring a T7 gn1 gene under the transcriptional control of the lacUV 5 promoter.

One strategy to maximize recombinant protein expression in *E. coli* is to express the protein in a host bacteria with an impaired capacity to proteolytically cleave the recombinant protein (Gottesman, p. 119-128, In *Gene Expression Technology: Methods in Enzymology* vol. 185, Academic Press, San Diego, CA, 1990. Another  
10 strategy is to alter the nucleic acid sequence of the nucleic acid to be inserted into an expression vector so that the individual codons for each amino acid are those preferentially utilized in *E. coli* (Wada *et al.*, 1992, *Nucleic Acids Res.* 20:2111-2118). Such alteration of nucleic acid sequences of the invention can be carried out by standard DNA synthesis techniques.

15 In another embodiment, the expression vector is a yeast expression vector. Examples of vectors for expression in yeast *S. cerevisiae* include pYepSec1 (Baldari *et al.*, 1987, *EMBO J.* 6:229-234), pMFa (Kurjan and Herskowitz, 1982, *Cell* 30:933-943), pJRY88 (Schultz *et al.*, 1987, *Gene* 54:113-123), pYES2 (Invitrogen Corporation, San Diego, CA), and pPicZ (Invitrogen Corp, San Diego, CA).

20 Alternatively, the expression vector is a baculovirus expression vector. Baculovirus vectors available for expression of proteins in cultured insect cells (*e.g.*, Sf 9 cells) include the pAc series (Smith *et al.*, 1983, *Mol. Cell Biol.* 3:2156-2165) and the pVL series (Lucklow and Summers, 1989, *Virology* 170:31-39).

In yet another embodiment, a nucleic acid of the invention is expressed in  
25 mammalian cells using a mammalian expression vector. Examples of mammalian expression vectors include pCDM8 (Seed, 1987, *Nature* 329:840) and pMT2PC (Kaufman *et al.*, 1987, *EMBO J.* 6:187-195). When used in mammalian cells, the expression vector's control functions are often provided by viral regulatory elements. For example, commonly used promoters are derived from polyoma, Adenovirus 2,  
30 cytomegalovirus and Simian Virus 40. For other suitable expression systems for both prokaryotic and eukaryotic cells see chapters 16 and 17 of Sambrook *et al.*, *supra*.

In another embodiment, the recombinant mammalian expression vector is capable of directing expression of the nucleic acid preferentially in a particular cell type (e.g., tissue-specific regulatory elements are used to express the nucleic acid). Tissue-specific regulatory elements are known in the art. Non-limiting examples of suitable  
5 tissue-specific promoters include the albumin promoter (liver-specific; Pinkert *et al.*, 1987, *Genes Dev.* 1:268-277), lymphoid-specific promoters (Calame and Eaton, 1988, *Adv. Immunol.* 43:235-275), in particular promoters of T cell receptors (Winoto and Baltimore, 1989, *EMBO J.* 8:729-733) and immunoglobulins (Banerji *et al.*, 1983, *Cell* 33:729-740; Queen and Baltimore, 1983, *Cell* 33:741-748), neuron-specific promoters  
10 (e.g., the neurofilament promoter; Byrne and Ruddle, 1989, *Proc. Natl. Acad. Sci. USA* 86:5473-5477), pancreas-specific promoters (Edlund *et al.*, 1985, *Science* 230:912-916), and mammary gland-specific promoters (e.g., milk whey promoter; U.S. Patent No. 4,873,316 and European Application Publication No. 264,166). Developmentally-regulated promoters are also encompassed, for example the murine hox promoters  
15 (Kessel and Gruss, 1990, *Science* 249:374-379) and the  $\alpha$ -fetoprotein promoter (Camper and Tilghman, 1989, *Genes Dev.* 3:537-546).

The invention further provides a recombinant expression vector comprising a DNA molecule of the invention cloned into the expression vector in an antisense orientation. That is, the DNA molecule is operably linked to a regulatory  
20 sequence in a manner which allows for expression (by transcription of the DNA molecule) of an RNA molecule which is antisense to the mRNA encoding a polypeptide of the invention. Regulatory sequences operably linked to a nucleic acid cloned in the antisense orientation can be chosen which direct the continuous expression of the antisense RNA molecule in a variety of cell types, for instance viral promoters and/or  
25 enhancers, or regulatory sequences can be chosen which direct constitutive, tissue-specific or cell type specific expression of antisense RNA. The antisense expression vector can be in the form of a recombinant plasmid, phagemid, or attenuated virus in which antisense nucleic acids are produced under the control of a high efficiency regulatory region, the activity of which can be determined by the cell type into which the  
30 vector is introduced. For a discussion of the regulation of gene expression using antisense genes see Weintraub *et al.*, 1986, *Trends in Genetics*, Vol. 1(1).

Another aspect of the invention pertains to host cells into which a recombinant expression vector of the invention has been introduced. The terms "host cell" and "recombinant host cell" are used interchangeably herein. It is understood that such terms refer not only to the particular subject cell but to the progeny or potential  
5 progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term as used herein.

A host cell can be any prokaryotic (*e.g.*, *E. coli*) or eukaryotic cell (*e.g.*,  
10 insect cells, yeast or mammalian cells).

Vector DNA can be introduced into prokaryotic or eukaryotic cells via conventional transformation or transfection techniques. As used herein, the terms "transformation" and "transfection" are intended to refer to a variety of art-recognized techniques for introducing foreign nucleic acid into a host cell, including calcium  
15 phosphate or calcium chloride co-precipitation, DEAE-dextran-mediated transfection, lipofection, or electroporation. Suitable methods for transforming or transfecting host cells can be found in Sambrook, *et al.* (*supra*), and other laboratory manuals.

For stable transfection of mammalian cells, it is known that, depending upon the expression vector and transfection technique used, only a small fraction of cells  
20 may integrate the foreign DNA into their genome. In order to identify and select these integrants, a gene that encodes a selectable marker (*e.g.*, for resistance to antibiotics) is generally introduced into the host cells along with the gene of interest. Preferred selectable markers include those which confer resistance to drugs, such as G418, hygromycin and methotrexate. Cells stably transfected with the introduced nucleic acid  
25 can be identified by drug selection (*e.g.*, cells that have incorporated the selectable marker will survive, while the other cells die).

A host cell of the invention, such as a prokaryotic or eukaryotic host cell in culture, can be used to produce a marker protein or a segment thereof. Accordingly, the invention further provides methods for producing a marker protein or a segment  
30 thereof using the host cells of the invention. In one embodiment, the method comprises culturing the host cell of the invention (into which a recombinant expression vector encoding a marker protein or a segment thereof has been introduced) in a suitable medium such that the is produced. In another embodiment, the method further

comprises isolating the marker protein or a segment thereof from the medium or the host cell.

The host cells of the invention can also be used to produce nonhuman transgenic animals. For example, in one embodiment, a host cell of the invention is a  
5 fertilized oocyte or an embryonic stem cell into which a sequences encoding a marker protein or a segment thereof have been introduced. Such host cells can then be used to create non-human transgenic animals in which exogenous sequences encoding a marker protein of the invention have been introduced into their genome or homologous recombinant animals in which endogenous gene(s) encoding a marker protein have been  
10 altered. Such animals are useful for studying the function and/or activity of the marker protein and for identifying and/or evaluating modulators of marker protein. As used herein, a "transgenic animal" is a non-human animal, preferably a mammal, more preferably a rodent such as a rat or mouse, in which one or more of the cells of the animal includes a transgene. Other examples of transgenic animals include non-human  
15 primates, sheep, dogs, cows, goats, chickens, amphibians, etc. A transgene is exogenous DNA which is integrated into the genome of a cell from which a transgenic animal develops and which remains in the genome of the mature animal, thereby directing the expression of an encoded gene product in one or more cell types or tissues of the transgenic animal. As used herein, an "homologous recombinant animal" is a non-  
20 human animal, preferably a mammal, more preferably a mouse, in which an endogenous gene has been altered by homologous recombination between the endogenous gene and an exogenous DNA molecule introduced into a cell of the animal, *e.g.*, an embryonic cell of the animal, prior to development of the animal.

A transgenic animal of the invention can be created by introducing a  
25 nucleic acid encoding a marker protein into the male pronuclei of a fertilized oocyte, *e.g.*, by microinjection, retroviral infection, and allowing the oocyte to develop in a pseudopregnant female foster animal. Intronic sequences and polyadenylation signals can also be included in the transgene to increase the efficiency of expression of the transgene. A tissue-specific regulatory sequence(s) can be operably linked to the  
30 transgene to direct expression of the polypeptide of the invention to particular cells. Methods for generating transgenic animals via embryo manipulation and microinjection, particularly animals such as mice, have become conventional in the art and are described, for example, in U.S. Patent Nos. 4,736,866 and 4,870,009, U.S. Patent No.



4,873,191 and in Hogan, *Manipulating the Mouse Embryo*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1986. Similar methods are used for production of other transgenic animals. A transgenic founder animal can be identified based upon the presence of the transgene in its genome and/or expression of mRNA  
5 encoding the transgene in tissues or cells of the animals. A transgenic founder animal can then be used to breed additional animals carrying the transgene. Moreover, transgenic animals carrying the transgene can further be bred to other transgenic animals carrying other transgenes.

To create an homologous recombinant animal, a vector is prepared which  
10 contains at least a portion of a gene encoding a marker protein into which a deletion, addition or substitution has been introduced to thereby alter, *e.g.*, functionally disrupt, the gene. In a preferred embodiment, the vector is designed such that, upon homologous recombination, the endogenous gene is functionally disrupted (*i.e.*, no longer encodes a functional protein; also referred to as a "knock out" vector). Alternatively, the vector  
15 can be designed such that, upon homologous recombination, the endogenous gene is mutated or otherwise altered but still encodes functional protein (*e.g.*, the upstream regulatory region can be altered to thereby alter the expression of the endogenous protein). In the homologous recombination vector, the altered portion of the gene is flanked at its 5' and 3' ends by additional nucleic acid of the gene to allow for  
20 homologous recombination to occur between the exogenous gene carried by the vector and an endogenous gene in an embryonic stem cell. The additional flanking nucleic acid sequences are of sufficient length for successful homologous recombination with the endogenous gene. Typically, several kilobases of flanking DNA (both at the 5' and 3' ends) are included in the vector (see, *e.g.*, Thomas and Capecchi, 1987, *Cell* 51:503 for a  
25 description of homologous recombination vectors). The vector is introduced into an embryonic stem cell line (*e.g.*, by electroporation) and cells in which the introduced gene has homologously recombined with the endogenous gene are selected (see, *e.g.*, Li *et al.*, 1992, *Cell* 69:915). The selected cells are then injected into a blastocyst of an animal (*e.g.*, a mouse) to form aggregation chimeras (see, *e.g.*, Bradley,  
30 *Teratocarcinomas and Embryonic Stem Cells: A Practical Approach*, Robertson, Ed., IRL, Oxford, 1987, pp. 113-152). A chimeric embryo can then be implanted into a suitable pseudopregnant female foster animal and the embryo brought to term. Progeny harboring the homologously recombined DNA in their germ cells can be used to breed

animals in which all cells of the animal contain the homologously recombined DNA by germline transmission of the transgene. Methods for constructing homologous recombination vectors and homologous recombinant animals are described further in Bradley (1991) *Current Opinion in Bio/Technology* 2:823-829 and in PCT Publication  
5 NOS. WO 90/11354, WO 91/01140, WO 92/0968, and WO 93/04169.

In another embodiment, transgenic non-human animals can be produced which contain selected systems which allow for regulated expression of the transgene. One example of such a system is the *cre/loxP* recombinase system of bacteriophage P1. For a description of the *cre/loxP* recombinase system, see, e.g., Lakso *et al.* (1992) *Proc.*  
10 *Natl. Acad. Sci. USA* 89:6232-6236. Another example of a recombinase system is the FLP recombinase system of *Saccharomyces cerevisiae* (O'Gorman *et al.*, 1991, *Science* 251:1351-1355). If a *cre/loxP* recombinase system is used to regulate expression of the transgene, animals containing transgenes encoding both the *Cre* recombinase and a  
selected protein are required. Such animals can be provided through the construction of  
15 "double" transgenic animals, e.g., by mating two transgenic animals, one containing a transgene encoding a selected protein and the other containing a transgene encoding a recombinase.

Clones of the non-human transgenic animals described herein can also be produced according to the methods described in Wilmut *et al.* (1997) *Nature* 385:810-  
20 813 and PCT Publication NOS. WO 97/07668 and WO 97/07669.

#### IV. Pharmaceutical Compositions

The nucleic acid molecules, polypeptides, and antibodies (also referred to herein as "active compounds") of the invention can be incorporated into pharmaceutical  
25 compositions suitable for administration. Such compositions typically comprise the nucleic acid molecule, protein, or antibody and a pharmaceutically acceptable carrier. As used herein the language "pharmaceutically acceptable carrier" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical  
30 administration. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the compositions is

contemplated. Supplementary active compounds can also be incorporated into the compositions.

The invention includes methods for preparing pharmaceutical compositions for modulating the expression or activity of a marker nucleic acid or protein. Such methods comprise formulating a pharmaceutically acceptable carrier with an agent which modulates expression or activity of a marker nucleic acid or protein. Such compositions can further include additional active agents. Thus, the invention further includes methods for preparing a pharmaceutical composition by formulating a pharmaceutically acceptable carrier with an agent which modulates expression or activity of a marker nucleic acid or protein and one or more additional active compounds.

The invention also provides methods (also referred to herein as "screening assays") for identifying modulators, *i.e.*, candidate or test compounds or agents (*e.g.*, peptides, peptidomimetics, peptoids, small molecules or other drugs) which (a) bind to the marker, or (b) have a modulatory (*e.g.*, stimulatory or inhibitory) effect on the activity of the marker or, more specifically, (c) have a modulatory effect on the interactions of the marker with one or more of its natural substrates (*e.g.*, peptide, protein, hormone, co-factor, or nucleic acid), or (d) have a modulatory effect on the expression of the marker. Such assays typically comprise a reaction between the marker and one or more assay components. The other components may be either the test compound itself, or a combination of test compound and a natural binding partner of the marker.

The test compounds of the present invention may be obtained from any available source, including systematic libraries of natural and/or synthetic compounds. Test compounds may also be obtained by any of the numerous approaches in combinatorial library methods known in the art, including: biological libraries; peptoid libraries (libraries of molecules having the functionalities of peptides, but with a novel, non-peptide backbone which are resistant to enzymatic degradation but which nevertheless remain bioactive; see, *e.g.*, Zuckermann *et al.*, 1994, *J. Med. Chem.* 37:2678-85); spatially addressable parallel solid phase or solution phase libraries; synthetic library methods requiring deconvolution; the 'one-bead one-compound' library method; and synthetic library methods using affinity chromatography selection. The biological library and peptoid library approaches are limited to peptide libraries, while

the other four approaches are applicable to peptide, non-peptide oligomer or small molecule libraries of compounds (Lam, 1997, *Anticancer Drug Des.* 12:145).

Examples of methods for the synthesis of molecular libraries can be found in the art, for example in: DeWitt *et al.* (1993) *Proc. Natl. Acad. Sci. U.S.A.* 90:6909; Erb *et al.* (1994) *Proc. Natl. Acad. Sci. USA* 91:11422; Zuckermann *et al.* (1994). *J. Med. Chem.* 37:2678; Cho *et al.* (1993) *Science* 261:1303; Carrell *et al.* (1994) *Angew. Chem. Int. Ed. Engl.* 33:2059; Carell *et al.* (1994) *Angew. Chem. Int. Ed. Engl.* 33:2061; and in Gallop *et al.* (1994) *J. Med. Chem.* 37:1233.

Libraries of compounds may be presented in solution (*e.g.*, Houghten, 1992, *Biotechniques* 13:412-421), or on beads (Lam, 1991, *Nature* 354:82-84), chips (Fodor, 1993, *Nature* 364:555-556), bacteria and/or spores, (Ladner, USP 5,223,409), plasmids (Cull *et al.*, 1992, *Proc Natl Acad Sci USA* 89:1865-1869) or on phage (Scott and Smith, 1990, *Science* 249:386-390; Devlin, 1990, *Science* 249:404-406; Cwirla *et al.*, 1990, *Proc. Natl. Acad. Sci.* 87:6378-6382; Felici, 1991, *J. Mol. Biol.* 222:301-310; Ladner, *supra.*).

In one embodiment, the invention provides assays for screening candidate or test compounds which are substrates of a protein encoded by or corresponding to a marker or biologically active portion thereof. In another embodiment, the invention provides assays for screening candidate or test compounds which bind to a protein encoded by or corresponding to a marker or biologically active portion thereof. Determining the ability of the test compound to directly bind to a protein can be accomplished, for example, by coupling the compound with a radioisotope or enzymatic label such that binding of the compound to the marker can be determined by detecting the labeled marker compound in a complex. For example, compounds (*e.g.*, marker substrates) can be labeled with  $^{125}\text{I}$ ,  $^{35}\text{S}$ ,  $^{14}\text{C}$ , or  $^3\text{H}$ , either directly or indirectly, and the radioisotope detected by direct counting of radioemission or by scintillation counting. Alternatively, assay components can be enzymatically labeled with, for example, horseradish peroxidase, alkaline phosphatase, or luciferase, and the enzymatic label detected by determination of conversion of an appropriate substrate to product.

In another embodiment, the invention provides assays for screening candidate or test compounds which modulate the expression of a marker or the activity of a protein encoded by or corresponding to a marker, or a biologically active portion

thereof. In all likelihood, the protein encoded by or corresponding to the marker can, *in vivo*, interact with one or more molecules, such as but not limited to, peptides, proteins, hormones, cofactors and nucleic acids. For the purposes of this discussion, such cellular and extracellular molecules are referred to herein as "binding partners" or marker  
5 "substrate".

One necessary embodiment of the invention in order to facilitate such screening is the use of a protein encoded by or corresponding to marker to identify the protein's natural *in vivo* binding partners. There are many ways to accomplish this which are known to one skilled in the art. One example is the use of the marker protein  
10 as "bait protein" in a two-hybrid assay or three-hybrid assay (see, *e.g.*, U.S. Patent No. 5,283,317; Zervos *et al*, 1993, *Cell* 72:223-232; Madura *et al*, 1993, *J. Biol. Chem.* 268:12046-12054; Bartel *et al*, 1993, *Biotechniques* 14:920-924; Iwabuchi *et al*, 1993 *Oncogene* 8:1693-1696; Brent WO94/10300) in order to identify other proteins which bind to or interact with the marker (binding partners) and, therefore, are possibly  
15 involved in the natural function of the marker. Such marker binding partners are also likely to be involved in the propagation of signals by the marker protein or downstream elements of a marker protein-mediated signaling pathway. Alternatively, such marker protein binding partners may also be found to be inhibitors of the marker protein.

The two-hybrid system is based on the modular nature of most  
20 transcription factors, which consist of separable DNA-binding and activation domains. Briefly, the assay utilizes two different DNA constructs. In one construct, the gene that encodes a marker protein fused to a gene encoding the DNA binding domain of a known transcription factor (*e.g.*, GAL-4). In the other construct, a DNA sequence, from a library of DNA sequences, that encodes an unidentified protein ("prey" or "sample") is  
25 fused to a gene that codes for the activation domain of the known transcription factor. If the "bait" and the "prey" proteins are able to interact, *in vivo*, forming a marker-dependent complex, the DNA-binding and activation domains of the transcription factor are brought into close proximity. This proximity allows transcription of a reporter gene (*e.g.*, LacZ) which is operably linked to a transcriptional regulatory site responsive to  
30 the transcription factor. Expression of the reporter gene can be readily detected and cell colonies containing the functional transcription factor can be isolated and used to obtain the cloned gene which encodes the protein which interacts with the marker protein.

In a further embodiment, assays may be devised through the use of the invention for the purpose of identifying compounds which modulate (*e.g.*, affect either positively or negatively) interactions between a marker protein and its substrates and/or binding partners. Such compounds can include, but are not limited to, molecules such as antibodies, peptides, hormones, oligonucleotides, nucleic acids, and analogs thereof. Such compounds may also be obtained from any available source, including systematic libraries of natural and/or synthetic compounds. The preferred assay components for use in this embodiment is an cervical cancer marker protein identified herein, the known binding partner and/or substrate of same, and the test compound. Test compounds can be supplied from any source.

The basic principle of the assay systems used to identify compounds that interfere with the interaction between the marker protein and its binding partner involves preparing a reaction mixture containing the marker protein and its binding partner under conditions and for a time sufficient to allow the two products to interact and bind, thus forming a complex. In order to test an agent for inhibitory activity, the reaction mixture is prepared in the presence and absence of the test compound. The test compound can be initially included in the reaction mixture, or can be added at a time subsequent to the addition of the marker protein and its binding partner. Control reaction mixtures are incubated without the test compound or with a placebo. The formation of any complexes between the marker protein and its binding partner is then detected. The formation of a complex in the control reaction, but less or no such formation in the reaction mixture containing the test compound, indicates that the compound interferes with the interaction of the marker protein and its binding partner. Conversely, the formation of more complex in the presence of compound than in the control reaction indicates that the compound may enhance interaction of the marker protein and its binding partner.

The assay for compounds that interfere with the interaction of the marker protein with its binding partner may be conducted in a heterogeneous or homogeneous format. Heterogeneous assays involve anchoring either the marker protein or its binding partner onto a solid phase and detecting complexes anchored to the solid phase at the end of the reaction. In homogeneous assays, the entire reaction is carried out in a liquid phase. In either approach, the order of addition of reactants can be varied to obtain different information about the compounds being tested. For example, test compounds

that interfere with the interaction between the marker proteins and the binding partners (e.g., by competition) can be identified by conducting the reaction in the presence of the test substance, *i.e.*, by adding the test substance to the reaction mixture prior to or simultaneously with the marker and its interactive binding partner. Alternatively, test compounds that disrupt preformed complexes, *e.g.*, compounds with higher binding constants that displace one of the components from the complex, can be tested by adding the test compound to the reaction mixture after complexes have been formed. The various formats are briefly described below.

In a heterogeneous assay system, either the marker protein or its binding partner is anchored onto a solid surface or matrix, while the other corresponding non-anchored component may be labeled, either directly or indirectly. In practice, microtitre plates are often utilized for this approach. The anchored species can be immobilized by a number of methods, either non-covalent or covalent, that are typically well known to one who practices the art. Non-covalent attachment can often be accomplished simply by coating the solid surface with a solution of the marker protein or its binding partner and drying. Alternatively, an immobilized antibody specific for the assay component to be anchored can be used for this purpose. Such surfaces can often be prepared in advance and stored.

In related embodiments, a fusion protein can be provided which adds a domain that allows one or both of the assay components to be anchored to a matrix. For example, glutathione-S-transferase/marker fusion proteins or glutathione-S-transferase/binding partner can be adsorbed onto glutathione sepharose beads (Sigma Chemical, St. Louis, MO) or glutathione derivatized microtiter plates, which are then combined with the test compound or the test compound and either the non-adsorbed marker or its binding partner, and the mixture incubated under conditions conducive to complex formation (*e.g.*, physiological conditions). Following incubation, the beads or microtiter plate wells are washed to remove any unbound assay components, the immobilized complex assessed either directly or indirectly, for example, as described above. Alternatively, the complexes can be dissociated from the matrix, and the level of marker binding or activity determined using standard techniques.

Other techniques for immobilizing proteins on matrices can also be used in the screening assays of the invention. For example, either a marker protein or a marker protein binding partner can be immobilized utilizing conjugation of biotin and

streptavidin. Biotinylated marker protein or target molecules can be prepared from biotin-NHS (N-hydroxy-succinimide) using techniques known in the art (*e.g.*, biotinylation kit, Pierce Chemicals, Rockford, IL), and immobilized in the wells of streptavidin-coated 96 well plates (Pierce Chemical). In certain embodiments, the  
5 protein-immobilized surfaces can be prepared in advance and stored.

In order to conduct the assay, the corresponding partner of the immobilized assay component is exposed to the coated surface with or without the test compound. After the reaction is complete, unreacted assay components are removed (*e.g.*, by washing) and any complexes formed will remain immobilized on the solid  
10 surface. The detection of complexes anchored on the solid surface can be accomplished in a number of ways. Where the non-immobilized component is pre-labeled, the detection of label immobilized on the surface indicates that complexes were formed. Where the non-immobilized component is not pre-labeled, an indirect label can be used to detect complexes anchored on the surface; *e.g.*, using a labeled antibody specific for  
15 the initially non-immobilized species (the antibody, in turn, can be directly labeled or indirectly labeled with, *e.g.*, a labeled anti-Ig antibody). Depending upon the order of addition of reaction components, test compounds which modulate (inhibit or enhance) complex formation or which disrupt preformed complexes can be detected.

In an alternate embodiment of the invention, a homogeneous assay may  
20 be used. This is typically a reaction, analogous to those mentioned above, which is conducted in a liquid phase in the presence or absence of the test compound. The formed complexes are then separated from unreacted components, and the amount of complex formed is determined. As mentioned for heterogeneous assay systems, the order of addition of reactants to the liquid phase can yield information about which test  
25 compounds modulate (inhibit or enhance) complex formation and which disrupt preformed complexes.

In such a homogeneous assay, the reaction products may be separated from unreacted assay components by any of a number of standard techniques, including but not limited to: differential centrifugation, chromatography, electrophoresis and  
30 immunoprecipitation. In differential centrifugation, complexes of molecules may be separated from uncomplexed molecules through a series of centrifugal steps, due to the different sedimentation equilibria of complexes based on their different sizes and densities (see, for example, Rivas, G., and Minton, A.P., *Trends Biochem Sci* 1993



Aug;18(8):284-7). Standard chromatographic techniques may also be utilized to separate complexed molecules from uncomplexed ones. For example, gel filtration chromatography separates molecules based on size, and through the utilization of an appropriate gel filtration resin in a column format, for example, the relatively larger complex may be separated from the relatively smaller uncomplexed components. Similarly, the relatively different charge properties of the complex as compared to the uncomplexed molecules may be exploited to differentially separate the complex from the remaining individual reactants, for example through the use of ion-exchange chromatography resins. Such resins and chromatographic techniques are well known to one skilled in the art (see, *e.g.*, Heegaard, 1998, *J Mol. Recognit.* 11:141-148; Hage and Tweed, 1997, *J. Chromatogr. B. Biomed. Sci. Appl.*, 699:499-525). Gel electrophoresis may also be employed to separate complexed molecules from unbound species (see, *e.g.*, Ausubel *et al* (eds.), In: Current Protocols in Molecular Biology, J. Wiley & Sons, New York, 1999). In this technique, protein or nucleic acid complexes are separated based on size or charge, for example. In order to maintain the binding interaction during the electrophoretic process, nondenaturing gels in the absence of reducing agent are typically preferred, but conditions appropriate to the particular interactants will be well known to one skilled in the art. Immunoprecipitation is another common technique utilized for the isolation of a protein-protein complex from solution (see, *e.g.*, Ausubel *et al* (eds.), In: Current Protocols in Molecular Biology, J. Wiley & Sons, New York, 1999). In this technique, all proteins binding to an antibody specific to one of the binding molecules are precipitated from solution by conjugating the antibody to a polymer bead that may be readily collected by centrifugation. The bound assay components are released from the beads (through a specific proteolysis event or other technique well known in the art which will not disturb the protein-protein interaction in the complex), and a second immunoprecipitation step is performed, this time utilizing antibodies specific for the correspondingly different interacting assay component. In this manner, only formed complexes should remain attached to the beads. Variations in complex formation in both the presence and the absence of a test compound can be compared, thus offering information about the ability of the compound to modulate interactions between the marker protein and its binding partner.

Also within the scope of the present invention are methods for direct detection of interactions between the marker protein and its natural binding partner and/or a test compound in a homogeneous or heterogeneous assay system without further sample manipulation. For example, the technique of fluorescence energy transfer  
5 may be utilized (see, *e.g.*, Lakowicz *et al*, U.S. Patent No. 5,631,169; Stavrianopoulos *et al*, U.S. Patent No. 4,868,103). Generally, this technique involves the addition of a fluorophore label on a first 'donor' molecule (*e.g.*, marker or test compound) such that its emitted fluorescent energy will be absorbed by a fluorescent label on a second, 'acceptor' molecule (*e.g.*, marker or test compound), which in turn is able to fluoresce  
10 due to the absorbed energy. Alternately, the 'donor' protein molecule may simply utilize the natural fluorescent energy of tryptophan residues. Labels are chosen that emit different wavelengths of light, such that the 'acceptor' molecule label may be differentiated from that of the 'donor'. Since the efficiency of energy transfer between the labels is related to the distance separating the molecules, spatial relationships  
15 between the molecules can be assessed. In a situation in which binding occurs between the molecules, the fluorescent emission of the 'acceptor' molecule label in the assay should be maximal. An FET binding event can be conveniently measured through standard fluorometric detection means well known in the art (*e.g.*, using a fluorimeter). A test substance which either enhances or hinders participation of one of the species in  
20 the preformed complex will result in the generation of a signal variant to that of background. In this way, test substances that modulate interactions between a marker and its binding partner can be identified in controlled assays.

In another embodiment, modulators of marker expression are identified in a method wherein a cell is contacted with a candidate compound and the expression  
25 of marker mRNA or protein in the cell, is determined. The level of expression of marker mRNA or protein in the presence of the candidate compound is compared to the level of expression of marker mRNA or protein in the absence of the candidate compound. The candidate compound can then be identified as a modulator of marker expression based on this comparison. For example, when expression of marker mRNA  
30 or protein is greater (statistically significantly greater) in the presence of the candidate compound than in its absence, the candidate compound is identified as a stimulator of marker mRNA or protein expression. Conversely, when expression of marker mRNA or protein is less (statistically significantly less) in the presence of the candidate compound

than in its absence, the candidate compound is identified as an inhibitor of marker mRNA or protein expression. The level of marker mRNA or protein expression in the cells can be determined by methods described herein for detecting marker mRNA or protein.

5                   In another aspect, the invention pertains to a combination of two or more of the assays described herein. For example, a modulating agent can be identified using a cell-based or a cell free assay, and the ability of the agent to modulate the activity of a marker protein can be further confirmed *in vivo*, *e.g.*, in a whole animal model for cellular transformation and/or tumorigenesis.

10                   This invention further pertains to novel agents identified by the above-described screening assays. Accordingly, it is within the scope of this invention to further use an agent identified as described herein in an appropriate animal model. For example, an agent identified as described herein (*e.g.*, a marker modulating agent, an antisense marker nucleic acid molecule, a marker-specific antibody, or a marker-binding  
15 partner) can be used in an animal model to determine the efficacy, toxicity, or side effects of treatment with such an agent. Alternatively, an agent identified as described herein can be used in an animal model to determine the mechanism of action of such an agent. Furthermore, this invention pertains to uses of novel agents identified by the above-described screening assays for treatments as described herein.

20                   It is understood that appropriate doses of small molecule agents and protein or polypeptide agents depends upon a number of factors within the knowledge of the ordinarily skilled physician, veterinarian, or researcher. The dose(s) of these agents will vary, for example, depending upon the identity, size, and condition of the subject or sample being treated, further depending upon the route by which the composition is to  
25 be administered, if applicable, and the effect which the practitioner desires the agent to have upon the nucleic acid or polypeptide of the invention. Exemplary doses of a small molecule include milligram or microgram amounts per kilogram of subject or sample weight (*e.g.* about 1 microgram per kilogram to about 500 milligrams per kilogram, about 100 micrograms per kilogram to about 5 milligrams per kilogram, or about 1  
30 microgram per kilogram to about 50 micrograms per kilogram). Exemplary doses of a protein or polypeptide include gram, milligram or microgram amounts per kilogram of subject or sample weight (*e.g.* about 1 microgram per kilogram to about 5 grams per kilogram, about 100 micrograms per kilogram to about 500 milligrams per kilogram, or

about 1 milligram per kilogram to about 50 milligrams per kilogram). It is furthermore understood that appropriate doses of one of these agents depend upon the potency of the agent with respect to the expression or activity to be modulated. Such appropriate doses can be determined using the assays described herein. When one or more of these agents is to be administered to an animal (*e.g.* a human) in order to modulate expression or activity of a polypeptide or nucleic acid of the invention, a physician, veterinarian, or researcher can, for example, prescribe a relatively low dose at first, subsequently increasing the dose until an appropriate response is obtained. In addition, it is understood that the specific dose level for any particular animal subject will depend upon a variety of factors including the activity of the specific agent employed, the age, body weight, general health, gender, and diet of the subject, the time of administration, the route of administration, the rate of excretion, any drug combination, and the degree of expression or activity to be modulated.

A pharmaceutical composition of the invention is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, *e.g.*, intravenous, intradermal, subcutaneous, oral (*e.g.*, inhalation), transdermal (topical), transmucosal, and rectal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediamine-tetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampules, disposable syringes or multiple dose vials made of glass or plastic.

Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL (BASF; Parsippany, NJ) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy

syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

15               Sterile injectable solutions can be prepared by incorporating the active compound (e.g., a polypeptide or antibody) in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle which contains a basic dispersion medium, and then incorporating the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying which yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

25               Oral compositions generally include an inert diluent or an edible carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed.

30               Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches, and the like can contain any of the following ingredients, or compounds of a similar nature: a

binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as  
5 peppermint, methyl salicylate, or orange flavoring.

For administration by inhalation, the compounds are delivered in the form of an aerosol spray from a pressurized container or dispenser which contains a suitable propellant, *e.g.*, a gas such as carbon dioxide, or a nebulizer.

Systemic administration can also be by transmucosal or transdermal  
10 means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal  
15 administration, the active compounds are formulated into ointments, salves, gels, or creams as generally known in the art.

The compounds can also be prepared in the form of suppositories (*e.g.*, with conventional suppository bases such as cocoa butter and other glycerides) or retention enemas for rectal delivery.

20 In one embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid.  
25 Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes having monoclonal antibodies incorporated therein or thereon) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled  
30 in the art, for example, as described in U.S. Patent No. 4,522,811.

It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the

subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active compound for the treatment of individuals.

For antibodies, the preferred dosage is 0.1 mg/kg to 100 mg/kg of body weight (generally 10 mg/kg to 20 mg/kg). If the antibody is to act in the brain, a dosage of 50 mg/kg to 100 mg/kg is usually appropriate. Generally, partially human antibodies and fully human antibodies have a longer half-life within the human body than other antibodies. Accordingly, lower dosages and less frequent administration is often possible. Modifications such as lipidation can be used to stabilize antibodies and to enhance uptake and tissue penetration (*e.g.*, into the cervical epithelium). A method for lipidation of antibodies is described by Cruikshank *et al.* (1997) *J. Acquired Immune Deficiency Syndromes and Human Retrovirology* 14:193.

The invention also provides vaccine compositions for the prevention and/or treatment of cervical cancer. The invention provides cervical cancer vaccine compositions in which a protein of a marker of Table 1, or a combination of proteins of the markers of Table 1, are introduced into a subject in order to stimulate an immune response against the cervical cancer. The invention also provides cervical cancer vaccine compositions in which a gene expression construct, which expresses a marker or fragment of a marker identified in Table 1, is introduced into the subject such that a protein or fragment of a protein encoded by a marker of Table 1 is produced by transfected cells in the subject at a higher than normal level and elicits an immune response.

In one embodiment, a cervical cancer vaccine is provided and employed as an immunotherapeutic agent for the prevention of cervical cancer. In another embodiment, a cervical cancer vaccine is provided and employed as an immunotherapeutic agent for the treatment of cervical cancer.

By way of example, a cervical cancer vaccine comprised of the proteins of the markers of Table 1, may be employed for the prevention and/or treatment of cervical cancer in a subject by administering the vaccine by a variety of routes, *e.g.*, intradermally, subcutaneously, or intramuscularly. In addition, the cervical cancer

vaccine can be administered together with adjuvants and/or immunomodulators to boost the activity of the vaccine and the subject's response. In one embodiment, devices and/or compositions containing the vaccine, suitable for sustained or intermittent release could be, implanted in the body or topically applied thereto for the relatively slow  
5 release of such materials into the body. The cervical cancer vaccine can be introduced along with immunomodulatory compounds, which can alter the type of immune response produced in order to produce a response which will be more effective in eliminating the cancer.

In another embodiment, a cervical cancer vaccine comprised of an  
10 expression construct of the markers of Table 1, may be introduced by injection into muscle or by coating onto microprojectiles and using a device designed for the purpose to fire the projectiles at high speed into the skin. The cells of the subject will then express the protein(s) or fragments of proteins of the markers of Table 1 and induce an immune  
15 response. In addition, the cervical cancer vaccine may be introduced along with expression constructs for immunomodulatory molecules, such as cytokines, which may increase the immune response or modulate the type of immune response produced in order to produce a response which will be more effective in eliminating the cancer.

The marker nucleic acid molecules can be inserted into vectors and used  
20 as gene therapy vectors. Gene therapy vectors can be delivered to a subject by, for example, intravenous injection, local administration (U.S. Patent 5,328,470), or by stereotactic injection (see, *e.g.*, Chen *et al.*, 1994, *Proc. Natl. Acad. Sci. USA* 91:3054-3057). The pharmaceutical preparation of the gene therapy vector can include the gene therapy vector in an acceptable diluent, or can comprise a slow release matrix in which  
25 the gene delivery vehicle is imbedded. Alternatively, where the complete gene delivery vector can be produced intact from recombinant cells, *e.g.* retroviral vectors, the pharmaceutical preparation can include one or more cells which produce the gene delivery system.

The pharmaceutical compositions can be included in a container, pack, or  
30 dispenser together with instructions for administration.



## V. Predictive Medicine

The present invention pertains to the field of predictive medicine in which diagnostic assays, prognostic assays, pharmacogenomics, and monitoring clinical trails are used for prognostic (predictive) purposes to thereby treat an individual prophylactically. Accordingly, one aspect of the present invention relates to diagnostic  
5 assays for determining the level of expression of one or more marker proteins or nucleic acids, in order to determine whether an individual is at risk of developing cervical cancer. Such assays can be used for prognostic or predictive purposes to thereby prophylactically treat an individual prior to the onset of the cancer.

10 Yet another aspect of the invention pertains to monitoring the influence of agents (*e.g.*, drugs or other compounds administered either to inhibit cervical cancer or to treat or prevent any other disorder {*i.e.* in order to understand any cervical carcinogenic effects that such treatment may have} ) on the expression or activity of a marker of the invention in clinical trials. These and other agents are described in further  
15 detail in the following sections.

### A. Diagnostic Assays

An exemplary method for detecting the presence or absence of a marker protein or nucleic acid in a biological sample involves obtaining a biological sample  
20 (*e.g.* a cervical-associated body fluid) from a test subject and contacting the biological sample with a compound or an agent capable of detecting the polypeptide or nucleic acid (*e.g.*, mRNA, genomic DNA, or cDNA). The detection methods of the invention can thus be used to detect mRNA, protein, cDNA, or genomic DNA, for example, in a biological sample *in vitro* as well as *in vivo*. For example, *in vitro* techniques for  
25 detection of mRNA include Northern hybridizations and *in situ* hybridizations. *In vitro* techniques for detection of a marker protein include enzyme linked immunosorbent assays (ELISAs), Western blots, immunoprecipitations and immunofluorescence. *In vitro* techniques for detection of genomic DNA include Southern hybridizations. Furthermore, *in vivo* techniques for detection of a marker protein include introducing  
30 into a subject a labeled antibody directed against the protein or fragment thereof. For example, the antibody can be labeled with a radioactive marker whose presence and location in a subject can be detected by standard imaging techniques.

A general principle of such diagnostic and prognostic assays involves preparing a sample or reaction mixture that may contain a marker, and a probe, under appropriate conditions and for a time sufficient to allow the marker and probe to interact and bind, thus forming a complex that can be removed and/or detected in the reaction mixture. These assays can be conducted in a variety of ways.

For example, one method to conduct such an assay would involve anchoring the marker or probe onto a solid phase support, also referred to as a substrate, and detecting target marker/probe complexes anchored on the solid phase at the end of the reaction. In one embodiment of such a method, a sample from a subject, which is to be assayed for presence and/or concentration of marker, can be anchored onto a carrier or solid phase support. In another embodiment, the reverse situation is possible, in which the probe can be anchored to a solid phase and a sample from a subject can be allowed to react as an unanchored component of the assay.

There are many established methods for anchoring assay components to a solid phase. These include, without limitation, marker or probe molecules which are immobilized through conjugation of biotin and streptavidin. Such biotinylated assay components can be prepared from biotin-NHS (N-hydroxy-succinimide) using techniques known in the art (*e.g.*, biotinylation kit, Pierce Chemicals, Rockford, IL), and immobilized in the wells of streptavidin-coated 96 well plates (Pierce Chemical). In certain embodiments, the surfaces with immobilized assay components can be prepared in advance and stored.

Other suitable carriers or solid phase supports for such assays include any material capable of binding the class of molecule to which the marker or probe belongs. Well-known supports or carriers include, but are not limited to, glass, polystyrene, nylon, polypropylene, nylon, polyethylene, dextran, amylases, natural and modified celluloses, polyacrylamides, gabbros, and magnetite.

In order to conduct assays with the above mentioned approaches, the non-immobilized component is added to the solid phase upon which the second component is anchored. After the reaction is complete, uncomplexed components may be removed (*e.g.*, by washing) under conditions such that any complexes formed will remain immobilized upon the solid phase. The detection of marker/probe complexes anchored to the solid phase can be accomplished in a number of methods outlined herein.

In a preferred embodiment, the probe, when it is the unanchored assay component, can be labeled for the purpose of detection and readout of the assay, either directly or indirectly, with detectable labels discussed herein and which are well-known to one skilled in the art.

5                   It is also possible to directly detect marker/probe complex formation without further manipulation or labeling of either component (marker or probe), for example by utilizing the technique of fluorescence energy transfer (see, for example, Lakowicz *et al.*, U.S. Patent No. 5,631,169; Stavrianopoulos, *et al.*, U.S. Patent No. 4,868,103). A fluorophore label on the first, 'donor' molecule is selected such that, upon  
10                   excitation with incident light of appropriate wavelength, its emitted fluorescent energy will be absorbed by a fluorescent label on a second 'acceptor' molecule, which in turn is able to fluoresce due to the absorbed energy. Alternately, the 'donor' protein molecule may simply utilize the natural fluorescent energy of tryptophan residues. Labels are chosen that emit different wavelengths of light, such that the 'acceptor' molecule label  
15                   may be differentiated from that of the 'donor'. Since the efficiency of energy transfer between the labels is related to the distance separating the molecules, spatial relationships between the molecules can be assessed. In a situation in which binding occurs between the molecules, the fluorescent emission of the 'acceptor' molecule label in the assay should be maximal. An FET binding event can be conveniently measured  
20                   through standard fluorometric detection means well known in the art (*e.g.*, using a fluorimeter).

                  In another embodiment, determination of the ability of a probe to recognize a marker can be accomplished without labeling either assay component (probe or marker) by utilizing a technology such as real-time Biomolecular Interaction Analysis  
25                   (BIA) (see, *e.g.*, Sjolander, S. and Urbaniczky, C., 1991, *Anal. Chem.* 63:2338-2345 and Szabo *et al.*, 1995, *Curr. Opin. Struct. Biol.* 5:699-705). As used herein, "BIA" or "surface plasmon resonance" is a technology for studying biospecific interactions in real time, without labeling any of the interactants (*e.g.*, BIAcore). Changes in the mass at the binding surface (indicative of a binding event) result in alterations of the refractive index  
30                   of light near the surface (the optical phenomenon of surface plasmon resonance (SPR)), resulting in a detectable signal which can be used as an indication of real-time reactions between biological molecules.

Alternatively, in another embodiment, analogous diagnostic and prognostic assays can be conducted with marker and probe as solutes in a liquid phase. In such an assay, the complexed marker and probe are separated from uncomplexed components by any of a number of standard techniques, including but not limited to:

5 differential centrifugation, chromatography, electrophoresis and immunoprecipitation. In differential centrifugation, marker/probe complexes may be separated from uncomplexed assay components through a series of centrifugal steps, due to the different sedimentation equilibria of complexes based on their different sizes and densities (see, for example, Rivas, G., and Minton, A.P., 1993, *Trends Biochem Sci.* 18(8):284-7).

10 Standard chromatographic techniques may also be utilized to separate complexed molecules from uncomplexed ones. For example, gel filtration chromatography separates molecules based on size, and through the utilization of an appropriate gel filtration resin in a column format, for example, the relatively larger complex may be separated from the relatively smaller uncomplexed components. Similarly, the relatively

15 different charge properties of the marker/probe complex as compared to the uncomplexed components may be exploited to differentiate the complex from uncomplexed components, for example through the utilization of ion-exchange chromatography resins. Such resins and chromatographic techniques are well known to one skilled in the art (see, *e.g.*, Heegaard, N.H., 1998, *J. Mol. Recognit.* Winter 11(1-6):141-8; Hage, D.S., and Tweed, S.A. *J Chromatogr B Biomed Sci Appl* 1997 Oct 20 10;699(1-2):499-525). Gel electrophoresis may also be employed to separate complexed assay components from unbound components (see, *e.g.*, Ausubel *et al.*, ed., *Current Protocols in Molecular Biology*, John Wiley & Sons, New York, 1987-1999). In this

25 technique, protein or nucleic acid complexes are separated based on size or charge, for example. In order to maintain the binding interaction during the electrophoretic process, non-denaturing gel matrix materials and conditions in the absence of reducing agent are typically preferred. Appropriate conditions to the particular assay and components thereof will be well known to one skilled in the art.

In a particular embodiment, the level of marker mRNA can be

30 determined both by *in situ* and by *in vitro* formats in a biological sample using methods known in the art. The term "biological sample" is intended to include tissues, cells, biological fluids and isolates thereof, isolated from a subject, as well as tissues, cells and fluids present within a subject. Many expression detection methods use isolated RNA.

For *in vitro* methods, any RNA isolation technique that does not select against the isolation of mRNA can be utilized for the purification of RNA from cervical cells (see, e.g., Ausubel *et al.*, ed., *Current Protocols in Molecular Biology*, John Wiley & Sons, New York 1987-1999). Additionally, large numbers of tissue samples can readily be  
5 processed using techniques well known to those of skill in the art, such as, for example, the single-step RNA isolation process of Chomczynski (1989, U.S. Patent No. 4,843,155).

The isolated mRNA can be used in hybridization or amplification assays that include, but are not limited to, Southern or Northern analyses, polymerase chain  
10 reaction analyses and probe arrays. One preferred diagnostic method for the detection of mRNA levels involves contacting the isolated mRNA with a nucleic acid molecule (probe) that can hybridize to the mRNA encoded by the gene being detected. The nucleic acid probe can be, for example, a full-length cDNA, or a portion thereof, such as an oligonucleotide of at least 7, 15, 30, 50, 100, 250 or 500 nucleotides in length and  
15 sufficient to specifically hybridize under stringent conditions to a mRNA or genomic DNA encoding a marker of the present invention. Other suitable probes for use in the diagnostic assays of the invention are described herein. Hybridization of an mRNA with the probe indicates that the marker in question is being expressed.

In one format, the mRNA is immobilized on a solid surface and contacted  
20 with a probe, for example by running the isolated mRNA on an agarose gel and transferring the mRNA from the gel to a membrane, such as nitrocellulose. In an alternative format, the probe(s) are immobilized on a solid surface and the mRNA is contacted with the probe(s), for example, in an Affymetrix gene chip array. A skilled artisan can readily adapt known mRNA detection methods for use in detecting the level  
25 of mRNA encoded by the markers of the present invention.

An alternative method for determining the level of mRNA marker in a sample involves the process of nucleic acid amplification, e.g., by rtPCR (the experimental embodiment set forth in Mullis, 1987, U.S. Patent No. 4,683,202), ligase chain reaction (Barany, 1991, *Proc. Natl. Acad. Sci. USA*, 88:189-193), self sustained  
30 sequence replication (Guatelli *et al.*, 1990, *Proc. Natl. Acad. Sci. USA* 87:1874-1878), transcriptional amplification system (Kwoh *et al.*, 1989, *Proc. Natl. Acad. Sci. USA* 86:1173-1177), Q-Beta Replicase (Lizardi *et al.*, 1988, *Bio/Technology* 6:1197), rolling circle replication (Lizardi *et al.*, U.S. Patent No. 5,854,033) or any other nucleic acid

amplification method, followed by the detection of the amplified molecules using techniques well known to those of skill in the art. These detection schemes are especially useful for the detection of nucleic acid molecules if such molecules are present in very low numbers. As used herein, amplification primers are defined as being  
5 a pair of nucleic acid molecules that can anneal to 5' or 3' regions of a gene (plus and minus strands, respectively, or vice-versa) and contain a short region in between. In general, amplification primers are from about 10 to 30 nucleotides in length and flank a region from about 50 to 200 nucleotides in length. Under appropriate conditions and with appropriate reagents, such primers permit the amplification of a nucleic acid  
10 molecule comprising the nucleotide sequence flanked by the primers.

For *in situ* methods, mRNA does not need to be isolated from the cervical cells prior to detection. In such methods, a cell or tissue sample is prepared/processed using known histological methods. The sample is then immobilized on a support, typically a glass slide, and then contacted with a probe that can hybridize to mRNA that  
15 encodes the marker.

As an alternative to making determinations based on the absolute expression level of the marker, determinations may be based on the normalized expression level of the marker. Expression levels are normalized by correcting the absolute expression level of a marker by comparing its expression to the expression of a  
20 gene that is not a marker, *e.g.*, a housekeeping gene that is constitutively expressed. Suitable genes for normalization include housekeeping genes such as the actin gene, or epithelial cell-specific genes. This normalization allows the comparison of the expression level in one sample, *e.g.*, a patient sample, to another sample, *e.g.*, a non-cervical cancer sample, or between samples from different sources.

Alternatively, the expression level can be provided as a relative expression level. To determine a relative expression level of a marker, the level of expression of the marker is determined for 10 or more samples of normal versus cancer cell isolates, preferably 50 or more samples, prior to the determination of the expression level for the sample in question. The mean expression level of each of the genes assayed  
25 in the larger number of samples is determined and this is used as a baseline expression level for the marker. The expression level of the marker determined for the test sample (absolute level of expression) is then divided by the mean expression value obtained for that marker. This provides a relative expression level.  
30

Preferably, the samples used in the baseline determination will be from cervical cancer or from non-cervical cancer cells of cervical tissue. The choice of the cell source is dependent on the use of the relative expression level. Using expression found in normal tissues as a mean expression score aids in validating whether the marker  
5 assayed is cervical specific (versus normal cells). In addition, as more data is accumulated, the mean expression value can be revised, providing improved relative expression values based on accumulated data. Expression data from cervical cells provides a means for grading the severity of the cervical cancer state.

In another embodiment of the present invention, a marker protein is  
10 detected. A preferred agent for detecting marker protein of the invention is an antibody capable of binding to such a protein or a fragment thereof, preferably an antibody with a detectable label. Antibodies can be polyclonal, or more preferably, monoclonal. An intact antibody, or a fragment or derivative thereof (*e.g.*, Fab or F(ab')<sub>2</sub>) can be used. The term "labeled", with regard to the probe or antibody, is intended to encompass direct  
15 labeling of the probe or antibody by coupling (*i.e.*, physically linking) a detectable substance to the probe or antibody, as well as indirect labeling of the probe or antibody by reactivity with another reagent that is directly labeled. Examples of indirect labeling include detection of a primary antibody using a fluorescently labeled secondary antibody and end-labeling of a DNA probe with biotin such that it can be detected with  
20 fluorescently labeled streptavidin.

Proteins from cervical cells can be isolated using techniques that are well known to those of skill in the art. The protein isolation methods employed can, for example, be such as those described in Harlow and Lane (Harlow and Lane, 1988, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring  
25 Harbor, New York).

A variety of formats can be employed to determine whether a sample contains a protein that binds to a given antibody. Examples of such formats include, but are not limited to, enzyme immunoassay (EIA), radioimmunoassay (RIA), Western blot analysis and enzyme linked immunoabsorbant assay (ELISA). A skilled artisan can  
30 readily adapt known protein/antibody detection methods for use in determining whether cervical cells express a marker of the present invention.

In one format, antibodies, or antibody fragments or derivatives, can be used in methods such as Western blots or immunofluorescence techniques to detect the expressed proteins. In such uses, it is generally preferable to immobilize either the antibody or proteins on a solid support. Suitable solid phase supports or carriers include  
5 any support capable of binding an antigen or an antibody. Well-known supports or carriers include glass, polystyrene, polypropylene, polyethylene, dextran, nylon, amylases, natural and modified celluloses, polyacrylamides, gabbros, and magnetite.

One skilled in the art will know many other suitable carriers for binding antibody or antigen, and will be able to adapt such support for use with the present  
10 invention. For example, protein isolated from cervical cells can be run on a polyacrylamide gel electrophoresis and immobilized onto a solid phase support such as nitrocellulose. The support can then be washed with suitable buffers followed by treatment with the detectably labeled antibody. The solid phase support can then be washed with the buffer a second time to remove unbound antibody. The amount of  
15 bound label on the solid support can then be detected by conventional means.

The invention also encompasses kits for detecting the presence of a marker protein or nucleic acid in a biological sample (*e.g.*, cervical smear). Such kits can be used to determine if a subject is suffering from or is at increased risk of developing cervical cancer. For example, the kit can comprise a labeled compound or  
20 agent capable of detecting a marker protein or nucleic acid in a biological sample and means for determining the amount of the protein or mRNA in the sample (*e.g.*, an antibody which binds the protein or a fragment thereof, or an oligonucleotide probe which binds to DNA or mRNA encoding the protein). Kits can also include instructions for interpreting the results obtained using the kit.

25 For antibody-based kits, the kit can comprise, for example: (1) a first antibody (*e.g.*, attached to a solid support) which binds to a marker protein; and, optionally, (2) a second, different antibody which binds to either the protein or the first antibody and is conjugated to a detectable label.

For oligonucleotide-based kits, the kit can comprise, for example: (1) an  
30 oligonucleotide, *e.g.*, a detectably labeled oligonucleotide, which hybridizes to a nucleic acid sequence encoding a marker protein or (2) a pair of primers useful for amplifying a marker nucleic acid molecule. The kit can also comprise, *e.g.*, a buffering agent, a preservative, or a protein stabilizing agent. The kit can further comprise components



necessary for detecting the detectable label (e.g., an enzyme or a substrate). The kit can also contain a control sample or a series of control samples which can be assayed and compared to the test sample. Each component of the kit can be enclosed within an individual container and all of the various containers can be within a single package,  
5 along with instructions for interpreting the results of the assays performed using the kit.

### B. Pharmacogenomics

The markers of the invention are also useful as pharmacogenomic markers. As used herein, a "pharmacogenomic marker" is an objective biochemical  
10 marker whose expression level correlates with a specific clinical drug response or susceptibility in a patient (see, e.g., McLeod *et al.* (1999) *Eur. J. Cancer* 35(12): 1650-1652). The presence or quantity of the pharmacogenomic marker expression is related to the predicted response of the patient and more particularly the patient's tumor to therapy with a specific drug or class of drugs. By assessing the presence or quantity of  
15 the expression of one or more pharmacogenomic markers in a patient, a drug therapy which is most appropriate for the patient, or which is predicted to have a greater degree of success, may be selected. For example, based on the presence or quantity of RNA or protein encoded by specific tumor markers in a patient, a drug or course of treatment may be selected that is optimized for the treatment of the specific tumor likely to be  
20 present in the patient. The use of pharmacogenomic markers therefore permits selecting or designing the most appropriate treatment for each cancer patient without trying different drugs or regimes.

Another aspect of pharmacogenomics deals with genetic conditions that alters the way the body acts on drugs. These pharmacogenetic conditions can occur  
25 either as rare defects or as polymorphisms. For example, glucose-6-phosphate dehydrogenase (G6PD) deficiency is a common inherited enzymopathy in which the main clinical complication is hemolysis after ingestion of oxidant drugs (anti-malarials, sulfonamides, analgesics, nitrofurans) and consumption of fava beans.

As an illustrative embodiment, the activity of drug metabolizing enzymes  
30 is a major determinant of both the intensity and duration of drug action. The discovery of genetic polymorphisms of drug metabolizing enzymes (e.g., N-acetyltransferase 2 (NAT 2) and cytochrome P450 enzymes CYP2D6 and CYP2C19) has provided an explanation as to why some patients do not obtain the expected drug effects or show

exaggerated drug response and serious toxicity after taking the standard and safe dose of a drug. These polymorphisms are expressed in two phenotypes in the population, the extensive metabolizer (EM) and poor metabolizer (PM). The prevalence of PM is different among different populations. For example, the gene coding for CYP2D6 is highly polymorphic and several mutations have been identified in PM, which all lead to the absence of functional CYP2D6. Poor metabolizers of CYP2D6 and CYP2C19 quite frequently experience exaggerated drug response and side effects when they receive standard doses. If a metabolite is the active therapeutic moiety, a PM will show no therapeutic response, as demonstrated for the analgesic effect of codeine mediated by its CYP2D6-formed metabolite morphine. The other extreme are the so called ultra-rapid metabolizers who do not respond to standard doses. Recently, the molecular basis of ultra-rapid metabolism has been identified to be due to CYP2D6 gene amplification.

Thus, the level of expression of a marker of the invention in an individual can be determined to thereby select appropriate agent(s) for therapeutic or prophylactic treatment of the individual. In addition, pharmacogenetic studies can be used to apply genotyping of polymorphic alleles encoding drug-metabolizing enzymes to the identification of an individual's drug responsiveness phenotype. This knowledge, when applied to dosing or drug selection, can avoid adverse reactions or therapeutic failure and thus enhance therapeutic or prophylactic efficiency when treating a subject with a modulator of expression of a marker of the invention.

### C. Monitoring Clinical Trials

Monitoring the influence of agents (*e.g.*, drug compounds) on the level of expression of a marker of the invention can be applied not only in basic drug screening, but also in clinical trials. For example, the effectiveness of an agent to affect marker expression can be monitored in clinical trials of subjects receiving treatment for cervical cancer. In a preferred embodiment, the present invention provides a method for monitoring the effectiveness of treatment of a subject with an agent (*e.g.*, an agonist, antagonist, peptidomimetic, protein, peptide, nucleic acid, small molecule, or other drug candidate) comprising the steps of (i) obtaining a pre-administration sample from a subject prior to administration of the agent; (ii) detecting the level of expression of one or more selected markers of the invention in the pre-administration sample; (iii) obtaining one or more post-administration samples from the subject; (iv) detecting the

level of expression of the marker(s) in the post-administration samples; (v) comparing the level of expression of the marker(s) in the pre-administration sample with the level of expression of the marker(s) in the post-administration sample or samples; and (vi) altering the administration of the agent to the subject accordingly. For example, increased expression of the marker gene(s) during the course of treatment may indicate ineffective dosage and the desirability of increasing the dosage. Conversely, decreased expression of the marker gene(s) may indicate efficacious treatment and no need to change dosage.

#### 10                    D. Electronic Apparatus Readable Media and Arrays

Electronic apparatus readable media comprising a marker of the present invention is also provided. As used herein, "electronic apparatus readable media" refers to any suitable medium for storing, holding or containing data or information that can be read and accessed directly by an electronic apparatus. Such media can include, but are not limited to: magnetic storage media, such as floppy discs, hard disc storage medium, and magnetic tape; optical storage media such as compact disc; electronic storage media such as RAM, ROM, EPROM, EEPROM and the like; general hard disks and hybrids of these categories such as magnetic/optical storage media. The medium is adapted or configured for having recorded thereon a marker of the present invention.

20                    As used herein, the term "electronic apparatus" is intended to include any suitable computing or processing apparatus or other device configured or adapted for storing data or information. Examples of electronic apparatus suitable for use with the present invention include stand-alone computing apparatus; networks, including a local area network (LAN), a wide area network (WAN) Internet, Intranet, and Extranet; electronic appliances such as a personal digital assistants (PDAs), cellular phone, pager and the like; and local and distributed processing systems.

As used herein, "recorded" refers to a process for storing or encoding information on the electronic apparatus readable medium. Those skilled in the art can readily adopt any of the presently known methods for recording information on known media to generate manufactures comprising the markers of the present invention.

30                    A variety of software programs and formats can be used to store the marker information of the present invention on the electronic apparatus readable medium. For example, the marker nucleic acid sequence can be represented in a word

processing text file, formatted in commercially-available software such as WordPerfect and MicroSoft Word, or represented in the form of an ASCII file, stored in a database application, such as DB2, Sybase, Oracle, or the like, as well as in other forms. Any number of data processor structuring formats (*e.g.*, text file or database) may be  
5 employed in order to obtain or create a medium having recorded thereon the markers of the present invention.

By providing the markers of the invention in readable form, one can routinely access the marker sequence information for a variety of purposes. For example, one skilled in the art can use the nucleotide or amino acid sequences of the  
10 present invention in readable form to compare a target sequence or target structural motif with the sequence information stored within the data storage means. Search means are used to identify fragments or regions of the sequences of the invention which match a particular target sequence or target motif.

The present invention therefore provides a medium for holding  
15 instructions for performing a method for determining whether a subject has cervical cancer or a pre-disposition to cervical cancer, wherein the method comprises the steps of determining the presence or absence of a marker and based on the presence or absence of the marker, determining whether the subject has cervical cancer or a pre-disposition to cervical cancer and/or recommending a particular treatment for cervical cancer or pre-  
20 cervical cancer condition.

The present invention further provides in an electronic system and/or in a network, a method for determining whether a subject has cervical cancer or a pre-disposition to cervical cancer associated with a marker wherein the method comprises the steps of determining the presence or absence of the marker, and based on the  
25 presence or absence of the marker, determining whether the subject has cervical cancer or a pre-disposition to cervical cancer, and/or recommending a particular treatment for the cervical cancer or pre-cervical cancer condition. The method may further comprise the step of receiving phenotypic information associated with the subject and/or acquiring from a network phenotypic information associated with the subject.

30 The present invention also provides in a network, a method for determining whether a subject has cervical cancer or a pre-disposition to cervical cancer associated with a marker, said method comprising the steps of receiving information associated with the marker receiving phenotypic information associated with the subject,

acquiring information from the network corresponding to the marker and/or cervical cancer, and based on one or more of the phenotypic information, the marker, and the acquired information, determining whether the subject has a cervical cancer or a pre-disposition to cervical cancer. The method may further comprise the step of  
5 recommending a particular treatment for the cervical cancer or pre-cervical cancer condition.

The present invention also provides a business method for determining whether a subject has cervical cancer or a pre-disposition to cervical cancer, said method comprising the steps of receiving information associated with the marker, receiving  
10 phenotypic information associated with the subject, acquiring information from the network corresponding to the marker and/or cervical cancer, and based on one or more of the phenotypic information, the marker, and the acquired information, determining whether the subject has cervical cancer or a pre-disposition to cervical cancer. The method may further comprise the step of recommending a particular treatment for the  
15 cervical cancer or pre-cervical cancer condition.

The invention also includes an array comprising a marker of the present invention. The array can be used to assay expression of one or more genes in the array. In one embodiment, the array can be used to assay gene expression in a tissue to ascertain tissue specificity of genes in the array. In this manner, up to about 7600 genes  
20 can be simultaneously assayed for expression. This allows a profile to be developed showing a battery of genes specifically expressed in one or more tissues.

In addition to such qualitative determination, the invention allows the quantitation of gene expression. Thus, not only tissue specificity, but also the level of expression of a battery of genes in the tissue is ascertainable. Thus, genes can be  
25 grouped on the basis of their tissue expression *per se* and level of expression in that tissue. This is useful, for example, in ascertaining the relationship of gene expression between or among tissues. Thus, one tissue can be perturbed and the effect on gene expression in a second tissue can be determined. In this context, the effect of one cell type on another cell type in response to a biological stimulus can be determined. Such a  
30 determination is useful, for example, to know the effect of cell-cell interaction at the level of gene expression. If an agent is administered therapeutically to treat one cell type but has an undesirable effect on another cell type, the invention provides an assay to determine the molecular basis of the undesirable effect and thus provides the

opportunity to co-administer a counteracting agent or otherwise treat the undesired effect. Similarly, even within a single cell type, undesirable biological effects can be determined at the molecular level. Thus, the effects of an agent on expression of other than the target gene can be ascertained and counteracted.

5                   In another embodiment, the array can be used to monitor the time course of expression of one or more genes in the array. This can occur in various biological contexts, as disclosed herein, for example development of cervical cancer, progression of cervical cancer, and processes, such a cellular transformation associated with cervical cancer.

10                   The array is also useful for ascertaining the effect of the expression of a gene on the expression of other genes in the same cell or in different cells. This provides, for example, for a selection of alternate molecular targets for therapeutic intervention if the ultimate or downstream target cannot be regulated.

                  The array is also useful for ascertaining differential expression patterns of  
15   one or more genes in normal and abnormal cells. This provides a battery of genes that could serve as a molecular target for diagnosis or therapeutic intervention.

#### E. Surrogate Markers

                  The markers of the invention may serve as surrogate markers for one or  
20   more disorders or disease states or for conditions leading up to disease states, and in particular, cervical cancer. As used herein, a "surrogate marker" is an objective biochemical marker which correlates with the absence or presence of a disease or disorder, or with the progression of a disease or disorder (*e.g.*, with the presence or absence of a tumor). The presence or quantity of such markers is independent of the  
25   disease. Therefore, these markers may serve to indicate whether a particular course of treatment is effective in lessening a disease state or disorder. Surrogate markers are of particular use when the presence or extent of a disease state or disorder is difficult to assess through standard methodologies (*e.g.*, early stage tumors), or when an assessment of disease progression is desired before a potentially dangerous clinical endpoint is  
30   reached (*e.g.*, an assessment of cardiovascular disease may be made using cholesterol levels as a surrogate marker, and an analysis of HIV infection may be made using HIV RNA levels as a surrogate marker, well in advance of the undesirable clinical outcomes of myocardial infarction or fully-developed AIDS). Examples of the use of surrogate

markers in the art include: Koomen *et al.* (2000) *J. Mass. Spectrom.* 35: 258-264; and James (1994) *AIDS Treatment News Archive* 209.

The markers of the invention are also useful as pharmacodynamic markers. As used herein, a “pharmacodynamic marker” is an objective biochemical marker which correlates specifically with drug effects. The presence or quantity of a pharmacodynamic marker is not related to the disease state or disorder for which the drug is being administered; therefore, the presence or quantity of the marker is indicative of the presence or activity of the drug in a subject. For example, a pharmacodynamic marker may be indicative of the concentration of the drug in a biological tissue, in that the marker is either expressed or transcribed or not expressed or transcribed in that tissue in relationship to the level of the drug. In this fashion, the distribution or uptake of the drug may be monitored by the pharmacodynamic marker. Similarly, the presence or quantity of the pharmacodynamic marker may be related to the presence or quantity of the metabolic product of a drug, such that the presence or quantity of the marker is indicative of the relative breakdown rate of the drug *in vivo*. Pharmacodynamic markers are of particular use in increasing the sensitivity of detection of drug effects, particularly when the drug is administered in low doses. Since even a small amount of a drug may be sufficient to activate multiple rounds of marker transcription or expression, the amplified marker may be in a quantity which is more readily detectable than the drug itself. Also, the marker may be more easily detected due to the nature of the marker itself; for example, using the methods described herein, antibodies may be employed in an immune-based detection system for a protein marker, or marker-specific radiolabeled probes may be used to detect a mRNA marker. Furthermore, the use of a pharmacodynamic marker may offer mechanism-based prediction of risk due to drug treatment beyond the range of possible direct observations. Examples of the use of pharmacodynamic markers in the art include: Matsuda *et al.* US 6,033,862; Hattis *et al.* (1991) *Env. Health Perspect.* 90: 229-238; Schentag (1999) *Am. J. Health-Syst. Pharm.* 56 Suppl. 3: S21-S24; and Nicolau (1999) *Am. J. Health-Syst. Pharm.* 56 Suppl. 3: S16-S20.

## VI. Experimental Protocol

### A. Identification of clones

Cervical tumor specific cDNA clones were identified by transcription profiling using mRNA from 12 cervical tumors, 5 CIN III, 5 CIN I and 12 normal  
5 cervical tissues. The subtracted libraries were constructed using mRNA from at least three independent normal ectocervix, B-lymphocytes, T-lymphocytes and other white blood cells (in activated and resting states) as drivers and four independent stage 1B cervical tumors or four independent CIN III cervical samples as testers. The top up-regulated clones in tumors or CIN III cervical tissues, as determined by proprietary  
10 statistical analysis methods, were selected. The clusters in which the selected clones belong were blasted against both public and proprietary sequence databases in order to identify other EST sequences or clusters with significant overlap. Thus, contiguous EST sequences and/or clusters were assembled into full-length genes.

An identification of protein sequence corresponding to the clone was  
15 accomplished by obtaining one of the following:

- a) a direct match between the protein sequence and at least one EST sequence in one of its 6 possible translations;
- b) a direct match between the nucleotide sequence for the mRNA corresponding to the protein sequence and at least one EST sequence;
- 20 c) a match between the protein sequence and a contiguous assembly (contig) of the EST sequences with other available EST sequences in the databases in one of its 6 possible translations; or
- d) a match between the nucleotide sequence for the mRNA corresponding to the protein sequence and a contiguous assembly of the EST sequences with other  
25 available EST sequences in the databases in one of its 6 possible translations.

## VII. Summary of the Data

Tables 1-3 list the markers obtained using the foregoing protocol. The tables provide the name of the gene corresponding to the marker ("Gene Name"), the  
30 sequence listing identifier of the cDNA sequence of a nucleotide transcript encoded by or corresponding to the marker ("SEQ ID NO (nts)"), the sequence listing identifier of the amino acid sequence of a protein encoded by the nucleotide transcript ("SEQ ID NO



(AAs”), and the location of the protein coding sequence within the cDNA sequence (“CDS”).

Table 1 lists all of the markers of the invention which are over-expressed in cervical cancer cells compared to normal (*i.e.*, non-cancerous) cervical cells. Table 2  
5 lists newly-identified nucleotide and amino acid sequences useful as cervical cancer markers. Table 3 lists newly-identified nucleotide sequences useful as cervical cancer markers.

#### Other Embodiments

10 Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims:

What is claimed:

1. An isolated nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1, 3, 5, 7, 143, 145, 147, 149, 151,  
5 167, 203, 217, 231, 233, 51, 65, 67, 68, 100, and 153.
2. A vector which contains the nucleic acid molecule of claim 1.
3. A host cell which contains the nucleic acid molecule of claim 1.
- 10 4. A method of assessing whether a patient is afflicted with cervical cancer, the method comprising comparing:
  - a) the level of expression of a marker in a patient sample, wherein the marker is selected from Table 1; and
  - 15 b) the normal level of expression of the marker in a control non-cervical cancer sample,wherein a significant increase in the level of expression of the marker in the patient sample and the normal level is an indication that the patient is afflicted with cervical cancer.
- 20 5. An isolated polypeptide which is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1, 3, 5, 7, 143, 145, 147, 149, 151, 167, 203, 217, 231, and 233.
- 25 6. An antibody which selectively binds to the polypeptide of claim 5.
7. An isolated polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 4, 6, 8, 144, 146, 148, 150, 152, 168, 204, 218, 232, and 234.
- 30 8. An antibody which selectively binds to the polypeptide of claim 7.

## SEQUENCE LISTING

<110> Millennium Pharmaceuticals, Inc. et al.

<120> NOVEL GENES, COMPOSITIONS, KITS, AND METHODS FOR  
IDENTIFICATION, ASSESSMENT, PREVENTION, AND THERAPY  
OF CERVICAL CANCER

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<150> US 60/298,159

<151> 2001-06-13

<150> US 60/298,155

<151> 2001-06-13

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12462

&lt;210&gt; 2

&lt;211&gt; 3907

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 2

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Leu	Ala	Gln	Phe	Arg	Gln	Arg	Lys	Ala	Gln	Ser	Asp	Gly	Gln	Ser	Pro
		20					25						30		
Ser	Lys	Lys	Gln	Lys	Lys	Lys	Arg	Lys	Thr	Ser	Ser	Ser	Lys	His	Asp
		35					40					45			
Val	Ser	Ala	His	His	Asp	Leu	Asn	Ile	Asp	Gln	Ser	Gln	Cys	Asn	Glu
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Met	Tyr	Ile	Asn	Ser	Ser	Gln	Arg	Val	Glu	Ser	Thr	Val	Ile	Pro	Glu
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Ser	Thr	Ile	Met	Arg	Thr	Leu	His	Ser	Gly	Glu	Ile	Thr	Ser	His	Glu
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Gln	Gly	Phe	Ser	Val	Glu	Leu	Glu	Ser	Glu	Ile	Ser	Thr	Thr	Ala	Asp
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Asp	Cys	Ser	Ser	Glu	Val	Asn	Gly	Cys	Ser	Phe	Val	Met	Arg	Thr	Gly
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Lys	Pro	Thr	Asn	Leu	Leu	Arg	Glu	Glu	Glu	Phe	Gly	Val	Asp	Asp	Ser
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Tyr	Ser	Glu	Gln	Gly	Ala	Gln	Asp	Ser	Pro	Thr	His	Leu	Glu	Met	Met
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Glu	Ser	Glu	Leu	Ala	Gly	Lys	Gln	His	Glu	Ile	Glu	Glu	Leu	Asn	Arg
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Glu	Leu	Glu	Glu	Met	Arg	Val	Thr	Tyr	Gly	Thr	Glu	Gly	Leu	Gln	Gln
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Gln	Phe	Gln	Gln	Leu	Gln	Ala	Ser	Glu	Thr	Leu	Arg	Asn	Ser	Thr	His
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Ala	His	Lys	Ser	Leu	Ser	Thr	Val	Glu	Asp	Leu	Lys	Ala	Glu	Ile	Val		
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Asn	Glu	Lys	Asp	Lys	Ala	Leu	Cys	Ser	Leu	Lys	Glu	Glu	Leu	Ile	Phe
			1140					1145					1150		
Ala	Gln	Glu	Glu	Lys	Ile	Lys	Glu	Leu	Gln	Lys	Ile	His	Gln	Leu	Glu
			1155				1160					1165			
Leu	Gln	Thr	Met	Lys	Thr	Gln	Glu	Thr	Gly	Asp	Glu	Gly	Lys	Pro	Leu
	1170					1175					1180				
His	Leu	Leu	Ile	Gly	Lys	Leu	Gln	Lys	Ala	Val	Ser	Glu	Glu	Cys	Ser
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Tyr	Phe	Leu	Gln	Thr	Leu	Cys	Ser	Val	Leu	Gly	Glu	Tyr	Tyr	Thr	Pro
				1205					1210					1215	
Ala	Leu	Lys	Cys	Glu	Val	Asn	Ala	Glu	Asp	Lys	Glu	Asn	Ser	Gly	Asp
			1220					1225					1230		
Tyr	Ile	Ser	Glu	Asn	Glu	Asp	Pro	Glu	Leu	Gln	Asp	Tyr	Arg	Tyr	Glu
			1235				1240					1245			
Val	Gln	Asp	Phe	Gln	Glu	Asn	Met	His	Thr	Leu	Leu	Asn	Lys	Val	Thr
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Trp	Gly	Gln	Gln	Thr	Asp	Gly	Met	Lys	Leu	Glu	Phe	Gly	Glu	Glu	Asn
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Asn	Leu	Glu	Asp	Ile	Asp	Val	Asn	His	Lys	Ser	Lys	Leu	Ser	Ser	Leu
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Gln	Asp	Leu	Glu	Lys	Thr	Lys	Leu	Glu	Glu	Gln	Val	Gln	Glu	Leu	Glu
			1330				1335				1340				
Ser	Leu	Ile	Ser	Ser	Leu	Gln	Gln	Gln	Leu	Lys	Glu	Thr	Glu	Gln	Asn

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Tyr Glu Ala Glu Ile His Cys Leu Gln Lys Arg Leu Gln Ala Val Ser						
	1365		1370		1375	
Glu Ser Thr Val Pro Pro Ser Leu Pro Val Asp Ser Val Val Ile Thr						
	1380		1385		1390	
Glu Ser Asp Ala Gln Arg Thr Met Tyr Pro Gly Ser Cys Val Lys Lys						
	1395		1400		1405	
Asn Ile Asp Gly Thr Ile Glu Phe Ser Gly Glu Phe Gly Val Lys Glu						
	1410		1415		1420	
Glu Thr Asn Ile Val Lys Leu Leu Glu Lys Gln Tyr Gln Glu Gln Leu						
	1425		1430		1435	
Glu Glu Glu Val Ala Lys Val Ile Val Ser Met Ser Ile Ala Phe Ala						
	1445		1450		1455	
Gln Gln Thr Glu Leu Ser Arg Ile Ser Gly Gly Lys Glu Asn Thr Ala						
	1460		1465		1470	
Ser Ser Lys Gln Ala His Ala Val Cys Gln Gln Glu Gln His Tyr Phe						
	1475		1480		1485	
Asn Glu Met Lys Leu Ser Gln Asp Gln Ile Gly Phe Gln Thr Phe Glu						
	1490		1495		1500	
Thr Val Asp Val Lys Phe Lys Glu Glu Phe Lys Pro Leu Ser Lys Glu						
	1505		1510		1515	
Leu Gly Glu His Gly Lys Glu Ile Leu Leu Ser Asn Ser Asp Pro His						
	1525		1530		1535	
Asp Ile Pro Glu Ser Lys Asp Cys Val Leu Thr Ile Ser Glu Glu Met						
	1540		1545		1550	
Phe Ser Lys Asp Lys Thr Phe Ile Val Arg Gln Ser Ile His Asp Glu						
	1555		1560		1565	
Ile Ser Val Ser Ser Met Asp Ala Ser Arg Gln Leu Met Leu Asn Glu						
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Glu Gln Leu Glu Asp Met Arg Gln Glu Leu Val Arg Gln Tyr Gln Glu						
	1585		1590		1595	
His Gln Gln Ala Thr Glu Leu Leu Arg Gln Ala His Met Arg Gln Met						
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Glu Arg Gln Arg Glu Asp Gln Glu Gln Leu Gln Glu Glu Ile Lys Arg						
	1620		1625		1630	
Leu Asn Arg Gln Leu Ala Gln Arg Ser Ser Ile Asp Asn Glu Asn Leu						
	1635		1640		1645	
Val Ser Glu Arg Glu Arg Val Leu Leu Glu Glu Leu Glu Ala Leu Lys						
	1650		1655		1660	
Gln Leu Ser Leu Ala Gly Arg Glu Lys Leu Cys Cys Glu Leu Arg Asn						
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Ser Ser Thr Gln Thr Gln Asn Gly Asn Glu Asn Gln Gly Glu Val Glu						
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Glu Gln Thr Phe Lys Glu Lys Glu Leu Asp Arg Lys Pro Glu Asp Val						
	1700		1705		1710	
Pro Pro Glu Ile Leu Ser Asn Glu Arg Tyr Ala Leu Gln Lys Ala Asn						
	1715		1720		1725	
Asn Arg Leu Leu Lys Ile Leu Leu Glu Val Val Lys Thr Thr Ala Ala						
	1730		1735		1740	
Val Glu Glu Thr Ile Gly Arg His Val Leu Gly Ile Leu Asp Arg Ser						
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Ser Lys Ser Gln Ser Ser Ala Ser Leu Ile Trp Arg Ser Glu Ala Glu						
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Ala Ser Val Lys Ser Cys Val His Glu Glu His Thr Arg Val Thr Asp						
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Glu Ser Ile Pro Ser Tyr Ser Gly Ser Asp Met Pro Arg Asn Asp Ile						
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Asn Met Trp Ser Lys Val Thr Glu Glu Gly Thr Glu Leu Ser Gln Arg						
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Gln Val Glu Thr Ala Asn Glu Glu Met Thr Phe Met Lys Asn Val Leu		2400
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Lys Glu Thr Asn Phe Lys Met Asn Gln Leu Thr Gln Glu Leu Phe Ser		
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Thr Tyr Phe Lys Ser Phe Glu Glu Asn Gly Lys Gly Ser Ile Ile Asn		
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Leu Glu Thr Arg Leu Leu Gln Leu Glu Ser Thr Val Ser Ala Lys Asp		
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Leu Glu Leu Thr Gln Cys Tyr Lys Gln Ile Lys Asp Met Gln Glu Gln		
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Gly Gln Phe Glu Thr Glu Met Leu Gln Lys Lys Ile Val Asn Leu Gln		
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Lys Ile Val Glu Glu Lys Val Ala Ala Ala Leu Val Ser Gln Ile Gln		
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Leu Glu Ala Val Gln Glu Tyr Ala Lys Phe Cys Gln Asp Asn Gln Thr		
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Ile Ser Ser Glu Pro Glu Arg Thr Asn Ile Gln Asn Leu Asn Gln Leu		
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&lt;211&gt; 12438

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 3

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&lt;211&gt; 3899

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 4

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Ser Lys Lys Gln Lys Lys Lys Arg Lys Thr Ser Ser Ser Lys His Asp
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Val Ser Ala His His Asp Leu Asn Ile Asp Gln Ser Gln Cys Asn Glu
50     55     60
Met Tyr Ile Asn Ser Ser Gln Arg Val Glu Ser Thr Val Ile Pro Glu
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Gln Gly Phe Ser Val Glu Leu Glu Ser Glu Ile Ser Thr Thr Ala Asp
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Glu Leu Glu Glu Met Arg Val Thr Tyr Gly Thr Glu Gly Leu Gln Gln
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Ser Ser Thr Ala Ala Asp Leu Leu Gln Ala Lys Gln Gln Ile Leu Thr
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His Gln Gln Gln Leu Glu Glu Gln Asp His Leu Leu Glu Asp Tyr Gln
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Lys Lys Lys Glu Asp Phe Thr Met Gln Ile Ser Phe Leu Gln Glu Lys
290    295    300
Ile Lys Val Tyr Glu Met Glu Gln Asp Lys Lys Val Glu Asn Ser Asn
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Lys Glu Glu Ile Gln Glu Lys Glu Thr Ile Ile Glu Glu Leu Asn Thr
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Lys Ile Ile Glu Glu Glu Lys Lys Thr Leu Glu Leu Lys Asp Lys Leu
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Thr Thr Ala Asp Lys Leu Leu Gly Glu Leu Gln Glu Gln Ile Val Gln
355    360    365

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Ser	Ala	Ser	Glu	Ser	Arg	Lys	Glu	Leu	Glu	Leu	Lys	His	Glu	Ala	Glu
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Val	Thr	Asn	Tyr	Lys	Ile	Lys	Leu	Glu	Met	Leu	Glu	Lys	Glu	Lys	Asn
		595					600					605			
Ala	Val	Leu	Asp	Arg	Met	Ala	Glu	Ser	Gln	Glu	Ala	Glu	Leu	Glu	Arg
610						615					620				
Leu	Arg	Thr	Gln	Leu	Leu	Phe	Ser	His	Glu	Glu	Glu	Leu	Ser	Lys	Leu
625					630					635					640
Lys	Glu	Asp	Leu	Glu	Ile	Glu	His	Arg	Ile	Asn	Ile	Glu	Lys	Leu	Lys
				645					650					655	
Asp	Asn	Leu	Gly	Ile	His	Tyr	Lys	Gln	Gln	Ile	Asp	Gly	Leu	Gln	Asn
			660					665					670		
Glu	Met	Ser	Gln	Lys	Ile	Glu	Thr	Met	Gln	Phe	Glu	Lys	Asp	Asn	Leu
			675				680					685			
Ile	Thr	Lys	Gln	Asn	Gln	Leu	Ile	Leu	Glu	Ile	Ser	Lys	Leu	Lys	Asp
690						695					700				
Leu	Gln	Gln	Ser	Leu	Val	Asn	Ser	Lys	Ser	Glu	Glu	Met	Thr	Leu	Gln
705					710					715					720
Ile	Asn	Glu	Leu	Gln	Lys	Glu	Ile	Glu	Ile	Leu	Arg	Gln	Glu	Glu	Lys
				725					730					735	
Glu	Lys	Gly	Thr	Leu	Glu	Gln	Glu	Val	Gln	Glu	Leu	Gln	Leu	Lys	Thr
			740					745					750		
Glu	Leu	Leu	Glu	Lys	Gln	Met	Lys	Glu	Lys	Glu	Asn	Asp	Leu	Gln	Glu
		755					760					765			
Lys	Phe	Ala	Gln	Leu	Glu	Ala	Glu	Asn	Ser	Ile	Leu	Lys	Asp	Glu	Lys
770						775					780				
Lys	Thr	Leu	Glu	Asp	Met	Leu	Lys	Ile	His	Thr	Pro	Val	Ser	Gln	Glu
785					790					795					800
Glu	Arg	Leu	Ile	Phe	Leu	Asp	Ser	Ile	Lys	Ser	Lys	Ser	Lys	Asp	Ser
				805					810					815	
Val	Trp	Glu	Lys	Glu	Ile	Glu	Ile	Leu	Ile	Glu	Glu	Asn	Glu	Asp	Leu
			820					825					830		
Lys	Gln	Gln	Cys	Ile	Gln	Leu	Asn	Glu	Glu	Ile	Glu	Lys	Gln	Arg	Asn

835	840	845
Thr Phe Ser Phe Ala Glu Lys Asn Phe Glu Val Asn Tyr Gln Glu Leu		
850	855	860
Gln Glu Glu Tyr Ala Cys Leu Leu Lys Val Lys Asp Asp Leu Glu Asp		
865	870	875
Ser Lys Asn Lys Gln Glu Leu Glu Tyr Lys Ser Lys Leu Lys Ala Leu		
885	890	895
Asn Glu Glu Leu His Leu Gln Arg Ile Asn Pro Thr Thr Val Lys Met		
900	905	910
Lys Ser Ser Val Phe Asp Glu Asp Lys Thr Phe Val Ala Glu Thr Leu		
915	920	925
Glu Met Gly Glu Val Val Glu Lys Asp Thr Thr Glu Leu Met Glu Lys		
930	935	940
Leu Glu Val Thr Lys Arg Glu Lys Leu Glu Leu Ser Gln Arg Leu Ser		
945	950	955
Asp Leu Ser Glu Gln Leu Lys Gln Lys His Gly Glu Ile Ser Phe Leu		
965	970	975
Asn Glu Glu Val Lys Ser Leu Lys Gln Glu Lys Glu Gln Val Ser Leu		
980	985	990
Arg Cys Arg Glu Leu Glu Ile Ile Ile Asn His Asn Arg Ala Glu Asn		
995	1000	1005
Val Gln Ser Cys Asp Thr Gln Val Ser Ser Leu Leu Asp Gly Val Val		
1010	1015	1020
Thr Met Thr Ser Arg Gly Ala Glu Gly Ser Val Ser Lys Val Asn Lys		
1025	1030	1035
Ser Phe Gly Glu Glu Ser Lys Ile Met Val Glu Asp Lys Val Ser Phe		
1045	1050	1055
Glu Asn Met Thr Val Gly Glu Glu Ser Lys Gln Glu Gln Leu Ile Leu		
1060	1065	1070
Asp His Leu Pro Ser Val Thr Lys Glu Ser Ser Leu Arg Ala Thr Gln		
1075	1080	1085
Pro Ser Glu Asn Asp Lys Leu Gln Lys Glu Leu Asn Val Leu Lys Ser		
1090	1095	1100
Glu Gln Asn Asp Leu Arg Leu Gln Met Glu Ala Gln Arg Ile Cys Leu		
1105	1110	1115
Ser Leu Val Tyr Ser Thr His Val Asp Gln Val Arg Glu Tyr Met Glu		
1125	1130	1135
Asn Glu Lys Asp Lys Ala Leu Cys Ser Leu Lys Glu Glu Leu Ile Phe		
1140	1145	1150
Ala Gln Glu Glu Lys Ile Lys Glu Leu Gln Lys Ile His Gln Leu Glu		
1155	1160	1165
Leu Gln Thr Met Lys Thr Gln Glu Thr Gly Asp Glu Gly Lys Pro Leu		
1170	1175	1180
His Leu Leu Ile Gly Lys Leu Gln Lys Ala Val Ser Glu Glu Cys Ser		
1185	1190	1195
Tyr Phe Leu Gln Thr Leu Cys Ser Val Leu Gly Glu Tyr Tyr Thr Pro		
1205	1210	1215
Ala Leu Lys Cys Glu Val Asn Ala Glu Asp Lys Glu Asn Ser Gly Asp		
1220	1225	1230
Tyr Ile Ser Glu Asn Glu Asp Pro Glu Leu Gln Asp Tyr Arg Tyr Glu		
1235	1240	1245
Val Gln Asp Phe Gln Glu Asn Met His Thr Leu Leu Asn Lys Val Thr		
1250	1255	1260
Glu Glu Tyr Asn Lys Leu Leu Val Leu Gln Thr Arg Leu Ser Lys Ile		
1265	1270	1275
Trp Gly Gln Gln Thr Asp Gly Met Lys Leu Glu Phe Gly Glu Glu Asn		
1285	1290	1295
Leu Pro Lys Glu Glu Thr Glu Phe Leu Ser Ile His Ser Gln Met Thr		
1300	1305	1310

Asn Leu Glu Asp Ile Asp Val Asn His Lys Ser Lys Leu Ser Ser Leu  
 1315 1320 1325  
 Gln Asp Leu Glu Lys Thr Lys Leu Glu Glu Gln Val Gln Glu Leu Glu  
 1330 1335 1340  
 Ser Leu Ile Ser Ser Leu Gln Gln Gln Leu Lys Glu Thr Glu Gln Asn  
 1345 1350 1355 1360  
 Tyr Glu Ala Glu Ile His Cys Leu Gln Lys Arg Leu Gln Ala Val Ser  
 1365 1370 1375  
 Glu Ser Thr Val Pro Pro Ser Leu Pro Val Asp Ser Val Val Ile Thr  
 1380 1385 1390  
 Glu Ser Asp Ala Gln Arg Thr Met Tyr Pro Gly Ser Cys Val Lys Lys  
 1395 1400 1405  
 Asn Ile Asp Gly Thr Ile Glu Phe Ser Gly Glu Phe Gly Val Lys Glu  
 1410 1415 1420  
 Glu Thr Asn Ile Val Lys Leu Leu Glu Lys Gln Tyr Gln Glu Gln Leu  
 1425 1430 1435 1440  
 Glu Glu Glu Val Ala Lys Val Ile Val Ser Met Ser Ile Ala Phe Ala  
 1445 1450 1455  
 Gln Gln Thr Glu Leu Ser Arg Ile Ser Gly Gly Lys Glu Asn Thr Ala  
 1460 1465 1470  
 Ser Ser Lys Gln Ala His Ala Val Cys Gln Gln Glu Gln His Tyr Phe  
 1475 1480 1485  
 Asn Glu Met Lys Leu Ser Gln Asp Gln Ile Gly Phe Gln Thr Phe Glu  
 1490 1495 1500  
 Thr Val Asp Val Lys Phe Lys Glu Glu Phe Lys Pro Leu Ser Lys Glu  
 1505 1510 1515 1520  
 Leu Gly Glu His Gly Lys Glu Ile Leu Leu Ser Asn Ser Asp Pro His  
 1525 1530 1535  
 Asp Ile Pro Glu Ser Lys Asp Cys Val Leu Thr Ile Ser Glu Glu Met  
 1540 1545 1550  
 Phe Ser Lys Asp Lys Thr Phe Ile Val Arg Gln Ser Ile His Asp Glu  
 1555 1560 1565  
 Ile Ser Val Ser Ser Met Asp Ala Ser Arg Gln Leu Met Leu Asn Glu  
 1570 1575 1580  
 Glu Gln Leu Glu Asp Met Arg Gln Glu Leu Val Arg Gln Tyr Gln Glu  
 1585 1590 1595 1600  
 His Gln Gln Ala Thr Glu Leu Leu Arg Gln Ala His Met Arg Gln Met  
 1605 1610 1615  
 Glu Arg Gln Arg Glu Asp Gln Glu Gln Leu Gln Glu Glu Ile Lys Arg  
 1620 1625 1630  
 Leu Asn Arg Gln Leu Ala Gln Arg Ser Ser Ile Asp Asn Glu Asn Leu  
 1635 1640 1645  
 Val Ser Glu Arg Glu Arg Val Leu Leu Glu Glu Leu Glu Ala Leu Lys  
 1650 1655 1660  
 Gln Leu Ser Leu Ala Gly Arg Glu Lys Leu Cys Cys Glu Leu Arg Asn  
 1665 1670 1675 1680  
 Ser Ser Thr Gln Thr Gln Asn Gly Asn Glu Asn Gln Gly Glu Val Glu  
 1685 1690 1695  
 Glu Gln Thr Phe Lys Glu Lys Glu Leu Asp Arg Lys Pro Glu Asp Val  
 1700 1705 1710  
 Pro Pro Glu Ile Leu Ser Asn Glu Arg Tyr Ala Leu Gln Lys Ala Asn  
 1715 1720 1725  
 Asn Arg Leu Leu Lys Ile Leu Leu Glu Val Val Lys Thr Thr Ala Ala  
 1730 1735 1740  
 Val Glu Glu Thr Ile Gly Arg His Val Leu Gly Ile Leu Asp Arg Ser  
 1745 1750 1755 1760  
 Ser Lys Ser Gln Ser Ser Ala Ser Leu Ile Trp Arg Ser Glu Ala Glu  
 1765 1770 1775  
 Ala Ser Val Lys Ser Cys Val His Glu Glu His Thr Arg Val Thr Asp

1780					1785					1790						
Glu	Ser	Ile	Pro	Ser	Tyr	Ser	Gly	Ser	Asp	Met	Pro	Arg	Asn	Asp	Ile	
1795					1800					1805						
Asn	Met	Trp	Ser	Lys	Val	Thr	Glu	Glu	Gly	Thr	Glu	Leu	Ser	Gln	Arg	
1810					1815					1820						
Leu	Val	Arg	Ser	Gly	Phe	Ala	Gly	Thr	Glu	Ile	Asp	Pro	Glu	Asn	Glu	
1825					1830					1835					1840	
Glu	Leu	Met	Leu	Asn	Ile	Ser	Ser	Arg	Leu	Gln	Ala	Ala	Val	Glu	Lys	
1845					1850					1855						
Leu	Leu	Glu	Ala	Ile	Ser	Glu	Thr	Ser	Ser	Gln	Leu	Glu	His	Ala	Lys	
1860					1865					1870						
Val	Thr	Gln	Thr	Glu	Leu	Met	Arg	Glu	Ser	Phe	Arg	Gln	Lys	Gln	Glu	
1875					1880					1885						
Ala	Thr	Glu	Ser	Leu	Lys	Cys	Gln	Glu	Glu	Leu	Arg	Glu	Arg	Leu	His	
1890					1895					1900						
Glu	Glu	Ser	Arg	Ala	Arg	Glu	Gln	Leu	Ala	Val	Glu	Leu	Ser	Lys	Ala	
1905					1910					1915					1920	
Glu	Gly	Val	Ile	Asp	Gly	Tyr	Ala	Asp	Glu	Lys	Thr	Leu	Phe	Glu	Arg	
1925					1930					1935						
Gln	Ile	Gln	Glu	Lys	Thr	Asp	Ile	Ile	Asp	Arg	Leu	Glu	Gln	Glu	Leu	
1940					1945					1950						
Leu	Cys	Ala	Ser	Asn	Arg	Leu	Gln	Glu	Leu	Glu	Ala	Glu	Gln	Gln	Gln	
1955					1960					1965						
Ile	Gln	Glu	Glu	Arg	Glu	Leu	Ser	Arg	Gln	Lys	Glu	Ala	Met	Lys		
1970					1975					1980						
Ala	Glu	Ala	Gly	Pro	Val	Glu	Gln	Gln	Leu	Leu	Gln	Glu	Thr	Glu	Lys	
1985					1990					1995					2000	
Leu	Met	Lys	Glu	Lys	Leu	Glu	Val	Gln	Cys	Gln	Ala	Glu	Lys	Val	Arg	
2005					2010					2015						
Asp	Asp	Leu	Gln	Lys	Gln	Val	Lys	Ala	Leu	Glu	Ile	Asp	Val	Glu	Glu	
2020					2025					2030						
Gln	Val	Ser	Arg	Phe	Ile	Glu	Leu	Glu	Gln	Glu	Lys	Asn	Thr	Glu	Leu	
2035					2040					2045						
Met	Asp	Leu	Arg	Gln	Gln	Asn	Gln	Ala	Leu	Glu	Lys	Gln	Leu	Glu	Lys	
2050					2055					2060						
Met	Arg	Lys	Phe	Leu	Asp	Glu	Gln	Ala	Ile	Asp	Arg	Glu	His	Glu	Arg	
2065					2070					2075					2080	
Asp	Val	Phe	Gln	Gln	Glu	Ile	Gln	Lys	Leu	Glu	Gln	Gln	Leu	Lys	Val	
2085					2090					2095						
Val	Pro	Arg	Phe	Gln	Pro	Ile	Ser	Glu	His	Gln	Thr	Arg	Glu	Val	Glu	
2100					2105					2110						
Gln	Leu	Ala	Asn	His	Leu	Lys	Glu	Lys	Thr	Asp	Lys	Cys	Ser	Glu	Leu	
2115					2120					2125						
Leu	Leu	Ser	Lys	Glu	Gln	Leu	Gln	Arg	Asp	Ile	Gln	Glu	Arg	Asn	Glu	
2130					2135					2140						
Glu	Ile	Glu	Lys	Leu	Glu	Phe	Arg	Val	Arg	Glu	Leu	Glu	Gln	Ala	Leu	
2145					2150					2155					2160	
Leu	Val	Glu	Asp	Arg	Lys	His	Phe	Gly	Ala	Val	Glu	Ala	Lys	Pro	Glu	
2165					2170					2175						
Leu	Ser	Leu	Glu	Val	Gln	Leu	Gln	Ala	Glu	Arg	Asp	Ala	Ile	Asp	Arg	
2180					2185					2190						
Lys	Glu	Lys	Glu	Ile	Thr	Asn	Leu	Glu	Glu	Gln	Leu	Glu	Gln	Phe	Arg	
2195					2200					2205						
Glu	Glu	Leu	Glu	Asn	Lys	Asn	Glu	Glu	Val	Gln	Gln	Leu	His	Met	Gln	
2210					2215					2220						
Leu	Glu	Ile	Gln	Lys	Lys	Glu	Ser	Thr	Thr	Arg	Leu	Gln	Glu	Leu	Glu	
2225					2230					2235					2240	
Gln	Glu	Asn	Lys	Leu	Phe	Lys	Asp	Asp	Met	Glu	Lys	Leu	Gly	Leu	Ala	
2245					2250					2255						

Ile Lys Glu Ser Asp Ala Met Ser Thr Gln Asp Gln His Val Leu Phe  
 2260 2265 2270  
 Gly Lys Phe Ala Gln Ile Ile Gln Glu Lys Glu Val Glu Ile Asp Gln  
 2275 2280 2285  
 Leu Asn Glu Gln Val Thr Lys Leu Gln Gln Gln Leu Lys Ile Thr Thr  
 2290 2295 2300  
 Asp Asn Lys Val Ile Glu Glu Lys Asn Glu Leu Ile Arg Asp Leu Glu  
 2305 2310 2315 2320  
 Thr Gln Ile Glu Cys Leu Met Ser Asp Gln Glu Cys Val Lys Arg Asn  
 2325 2330 2335  
 Arg Glu Glu Glu Ile Glu Gln Leu Asn Glu Val Ile Glu Lys Leu Gln  
 2340 2345 2350  
 Gln Glu Leu Ala Asn Ile Gly Gln Lys Thr Ser Met Asn Ala His Ser  
 2355 2360 2365  
 Leu Ser Glu Glu Ala Asp Ser Leu Lys His Gln Leu Asp Val Val Ile  
 2370 2375 2380  
 Ala Glu Lys Leu Ala Leu Glu Gln Gln Val Glu Thr Ala Asn Glu Glu  
 2385 2390 2395 2400  
 Met Thr Phe Met Lys Asn Val Leu Lys Glu Thr Asn Phe Lys Met Asn  
 2405 2410 2415  
 Gln Leu Thr Gln Glu Leu Phe Ser Leu Lys Arg Glu Arg Glu Ser Val  
 2420 2425 2430  
 Glu Lys Ile Gln Ser Ile Pro Glu Asn Ser Val Asn Val Ala Ile Asp  
 2435 2440 2445  
 His Leu Ser Lys Asp Lys Pro Glu Leu Glu Val Val Leu Thr Glu Asp  
 2450 2455 2460  
 Ala Leu Lys Ser Leu Glu Asn Gln Thr Tyr Phe Lys Ser Phe Glu Glu  
 2465 2470 2475 2480  
 Asn Gly Lys Gly Ser Ile Ile Asn Leu Glu Thr Arg Leu Leu Gln Leu  
 2485 2490 2495  
 Glu Ser Thr Val Ser Ala Lys Asp Leu Glu Leu Thr Gln Cys Tyr Lys  
 2500 2505 2510  
 Gln Ile Lys Asp Met Gln Glu Gln Gly Gln Phe Glu Thr Glu Met Leu  
 2515 2520 2525  
 Gln Lys Lys Ile Val Asn Leu Gln Lys Ile Val Glu Glu Lys Val Ala  
 2530 2535 2540  
 Ala Ala Leu Val Ser Gln Ile Gln Leu Glu Ala Val Gln Glu Tyr Ala  
 2545 2550 2555 2560  
 Lys Phe Cys Gln Asp Asn Gln Thr Ile Ser Ser Glu Pro Glu Arg Thr  
 2565 2570 2575  
 Asn Ile Gln Asn Leu Asn Gln Leu Arg Glu Asp Glu Leu Gly Ser Asp  
 2580 2585 2590  
 Ile Ser Ala Leu Thr Leu Arg Ile Ser Glu Leu Glu Ser Gln Val Val  
 2595 2600 2605  
 Glu Met His Thr Ser Leu Ile Leu Glu Lys Glu Gln Val Glu Ile Ala  
 2610 2615 2620  
 Glu Lys Asn Val Leu Glu Lys Glu Lys Lys Leu Leu Glu Leu Gln Lys  
 2625 2630 2635 2640  
 Leu Leu Glu Gly Asn Glu Lys Lys Gln Arg Glu Lys Glu Lys Lys Arg  
 2645 2650 2655  
 Ser Pro Gln Asp Val Glu Val Leu Lys Thr Thr Thr Glu Leu Phe His  
 2660 2665 2670  
 Ser Asn Glu Glu Ser Gly Phe Phe Asn Glu Leu Glu Ala Leu Arg Ala  
 2675 2680 2685  
 Glu Ser Val Ala Thr Lys Ala Glu Leu Ala Ser Tyr Lys Glu Lys Ala  
 2690 2695 2700  
 Glu Lys Leu Gln Glu Glu Leu Leu Val Lys Glu Thr Asn Met Thr Ser  
 2705 2710 2715 2720  
 Leu Gln Lys Asp Leu Ser Gln Val Arg Asp His Leu Ala Glu Ala Lys



										2725											2730											2735
Glu	Lys	Leu	Ser	Ile	Leu	Glu	Lys	Glu	Asp	Glu	Thr	Glu	Val	Gln	Glu																	
										2740											2745											2750
Ser	Lys	Lys	Ala	Cys	Met	Phe	Glu	Pro	Leu	Pro	Ile	Lys	Leu	Ser	Lys																	
										2755											2760											2765
Ser	Ile	Ala	Ser	Gln	Thr	Asp	Gly	Thr	Leu	Lys	Ile	Ser	Ser	Ser	Asn																	
										2770											2775											2780
Gln	Thr	Pro	Gln	Ile	Leu	Val	Lys	Asn	Ala	Gly	Ile	Gln	Ile	Asn	Leu																	
										2785											2790											2795
Gln	Ser	Glu	Cys	Ser	Ser	Glu	Glu	Val	Thr	Glu	Ile	Ile	Ser	Gln	Phe																	
										2805											2810											2815
Thr	Glu	Lys	Ile	Glu	Lys	Met	Gln	Glu	Leu	His	Ala	Ala	Glu	Ile	Leu																	
										2820											2825											2830
Asp	Met	Glu	Ser	Arg	His	Ile	Ser	Glu	Thr	Glu	Thr	Leu	Lys	Arg	Glu																	
										2835											2840											2845
His	Tyr	Val	Ala	Val	Gln	Leu	Lys	Glu	Glu	Cys	Gly	Thr	Leu	Lys																		
										2850											2855											2860
Ala	Val	Ile	Gln	Cys	Leu	Arg	Ser	Lys	Glu	Gly	Ser	Ser	Ile	Pro	Glu																	
										2865											2870											2875
Leu	Ala	His	Ser	Asp	Ala	Tyr	Gln	Thr	Arg	Glu	Ile	Cys	Ser	Ser	Asp																	
										2885											2890											2895
Ser	Gly	Ser	Asp	Trp	Gly	Gln	Gly	Ile	Tyr	Leu	Thr	His	Ser	Gln	Gly																	
										2900											2905											2910
Phe	Asp	Ile	Ala	Ser	Glu	Gly	Arg	Gly	Glu	Glu	Ser	Glu	Ser	Ala	Thr																	
										2915											2920											2925
Asp	Ser	Phe	Pro	Lys	Lys	Ile	Lys	Gly	Leu	Leu	Arg	Ala	Val	His	Asn																	
										2930											2935											2940
Glu	Gly	Met	Gln	Val	Leu	Ser	Leu	Thr	Glu	Ser	Pro	Tyr	Ser	Asp	Gly																	
										2945											2950											2955
Glu	Asp	His	Ser	Ile	Gln	Gln	Val	Ser	Glu	Pro	Trp	Leu	Glu	Glu	Arg																	
										2965											2970											2975
Lys	Ala	Tyr	Ile	Asn	Thr	Ile	Ser	Ser	Leu	Lys	Asp	Leu	Ile	Thr	Lys																	
										2980											2985											2990
Met	Gln	Leu	Gln	Arg	Glu	Ala	Glu	Val	Tyr	Asp	Ser	Ser	Gln	Ser	His																	
										2995											3000											3005
Glu	Ser	Phe	Ser	Asp	Trp	Arg	Gly	Glu	Leu	Leu	Leu	Ala	Leu	Gln	Gln																	
										3010											3015											3020
Val	Phe	Leu	Glu	Glu	Arg	Ser	Val	Leu	Leu	Ala	Ala	Phe	Arg	Thr	Glu																	
										3025											3030											3035
Leu	Thr	Ala	Leu	Gly	Thr	Thr	Asp	Ala	Val	Gly	Leu	Leu	Asn	Cys	Leu																	
										3045											3050											3055
Glu	Gln	Arg	Ile	Gln	Glu	Gln	Gly	Val	Glu	Tyr	Gln	Ala	Ala	Met	Glu																	
										3060											3065											3070
Cys	Leu	Gln	Lys	Ala	Asp	Arg	Arg	Ser	Leu	Leu	Ser	Glu	Ile	Gln	Ala																	
										3075											3080											3085
Leu	His	Ala	Gln	Met	Asn	Gly	Arg	Lys	Ile	Thr	Leu	Lys	Arg	Glu	Gln																	
										3090											3095											3100
Glu	Ser	Glu	Lys	Pro	Ser	Gln	Glu	Leu	Leu	Glu	Tyr	Asn	Ile	Gln	Gln																	
										3105											3110											3115
Lys	Gln	Ser	Gln	Met	Leu	Glu	Met	Gln	Val	Glu	Leu	Ser	Ser	Met	Lys																	
										3125											3130											3135
Asp	Arg	Ala	Thr	Glu	Leu	Gln	Glu	Gln	Leu	Ser	Ser	Glu	Lys	Met	Val																	
										3140											3145											3150
Val	Ala	Glu	Leu	Lys	Ser	Glu	Leu	Ala	Gln	Thr	Lys	Leu	Glu	Leu	Glu																	
										3155											3160											3165
Thr	Thr	Leu	Lys	Ala	Gln	His	Lys	His	Leu	Lys	Glu	Leu	Glu	Ala	Phe																	
										3170											3175											3180
Arg	Leu	Glu	Val	Lys	Asp	Lys	Thr	Asp	Glu	Val	His	Leu	Leu	Asn	Asp																	
										3185											3190											3195
																																3200

Thr Leu Ala Ser. Glu Gln Lys Lys Ser Arg Glu Leu Gln Trp Ala Leu  
 3205 3210 3215  
 Glu Lys Glu Lys Ala Lys Leu Gly Arg Ser Glu Glu Arg Asp Lys Glu  
 3220 3225 3230  
 Glu Leu Glu Asp Leu Lys Phe Ser Leu Glu Ser Gln Lys Gln Arg Asn  
 3235 3240 3245  
 Leu Gln Leu Asn Leu Leu Leu Glu Gln Gln Lys Gln Leu Leu Asn Glu  
 3250 3255 3260  
 Ser Gln Gln Lys Ile Glu Ser Gln Arg Met Leu Tyr Asp Ala Gln Leu  
 3265 3270 3275 3280  
 Ser Glu Glu Gln Gly Arg Asn Leu Glu Leu Gln Val Leu Leu Glu Ser  
 3285 3290 3295  
 Glu Lys Val Arg Ile Arg Glu Met Ser Ser Thr Leu Asp Arg Glu Arg  
 3300 3305 3310  
 Glu Leu His Ala Gln Leu Gln Ser Ser Asp Gly Thr Gly Gln Ser Arg  
 3315 3320 3325  
 Pro Pro Leu Pro Ser Glu Asp Leu Leu Lys Glu Leu Gln Lys Gln Leu  
 3330 3335 3340  
 Glu Glu Lys His Ser Arg Ile Val Glu Leu Leu Asn Glu Thr Glu Lys  
 3345 3350 3355 3360  
 Tyr Lys Leu Asp Ser Leu Gln Thr Arg Gln Gln Met Glu Lys Asp Arg  
 3365 3370 3375  
 Gln Val His Arg Lys Thr Leu Gln Thr Glu Gln Glu Ala Asn Thr Glu  
 3380 3385 3390  
 Gly Gln Lys Lys Met His Glu Leu Gln Ser Lys Val Glu Asp Leu Gln  
 3395 3400 3405  
 Arg Gln Leu Glu Glu Lys Arg Gln Gln Val Tyr Lys Leu Asp Leu Glu  
 3410 3415 3420  
 Gly Gln Arg Leu Gln Gly Ile Met Gln Glu Phe Gln Lys Gln Glu Leu  
 3425 3430 3435 3440  
 Glu Arg Glu Glu Lys Arg Glu Ser Arg Arg Ile Leu Tyr Gln Asn Leu  
 3445 3450 3455  
 Asn Glu Pro Thr Thr Trp Ser Leu Thr Ser Asp Arg Thr Arg Asn Trp  
 3460 3465 3470  
 Val Leu Gln Gln Lys Ile Glu Gly Glu Thr Lys Glu Ser Asn Tyr Ala  
 3475 3480 3485  
 Lys Leu Ile Glu Met Asn Gly Gly Gly Thr Gly Cys Asn His Glu Leu  
 3490 3495 3500  
 Glu Met Ile Arg Gln Lys Leu Gln Cys Val Ala Ser Lys Leu Gln Val  
 3505 3510 3515 3520  
 Leu Pro Gln Lys Ala Ser Glu Arg Leu Gln Phe Glu Thr Ala Asp Asp  
 3525 3530 3535  
 Glu Asp Phe Ile Trp Val Gln Glu Asn Ile Asp Glu Ile Ile Leu Gln  
 3540 3545 3550  
 Leu Gln Lys Leu Thr Gly Gln Gln Gly Glu Glu Pro Ser Leu Val Ser  
 3555 3560 3565  
 Pro Ser Thr Ser Cys Gly Ser Leu Thr Glu Arg Leu Leu Arg Gln Asn  
 3570 3575 3580  
 Ala Glu Leu Thr Gly His Ile Ser Gln Leu Thr Glu Glu Lys Asn Asp  
 3585 3590 3595 3600  
 Leu Arg Asn Met Val Met Lys Leu Glu Glu Gln Ile Arg Trp Tyr Arg  
 3605 3610 3615  
 Gln Thr Gly Ala Gly Arg Asp Asn Ser Ser Arg Phe Ser Leu Asn Gly  
 3620 3625 3630  
 Gly Ala Asn Ile Glu Ala Ile Ile Ala Ser Glu Lys Glu Val Trp Asn  
 3635 3640 3645  
 Arg Glu Lys Leu Thr Leu Gln Lys Ser Leu Lys Arg Ala Glu Ala Glu  
 3650 3655 3660  
 Val Tyr Lys Leu Lys Ala Glu Leu Arg Asn Asp Ser Leu Leu Gln Thr

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Tyr Leu Leu Leu Leu Leu Gly Gly Phe Gln Glu Cys Glu Asp Ala Thr						
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Leu Ala Leu Leu Ala Arg Met Gly Gly Gln Pro Ala Phe Thr Asp Leu						
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Glu Val Ile Thr Asn Arg Pro Lys Gly Phe Thr Arg Phe Arg Ser Ala						
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Val Arg Val Ser Ile Ala Ile Ser Arg Met Lys Phe Leu Val Arg Arg						
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Trp His Arg Val Thr Gly Ser Val Ser Ile Asn Ile Asn Arg Asp Gly						
	3780		3785		3790	
Phe Gly Leu Asn Gln Gly Ala Glu Lys Thr Asp Ser Phe Tyr His Ser						
	3795		3800		3805	
Ser Gly Gly Leu Glu Leu Tyr Gly Glu Pro Arg His Thr Thr Tyr Arg						
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Ser Arg Ser Asp Leu Asp Tyr Ile Arg Ser Pro Leu Pro Phe Gln Asn						
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Arg Tyr Pro Gly Thr Pro Ala Asp Phe Asn Pro Gly Ser Leu Ala Cys						
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Ser Gln Leu Gln Asn Tyr Asp Pro Asp Arg Ala Leu Thr Asp Tyr Ile						
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Thr Arg Leu Glu Ala Leu Gln Arg Arg Leu Gly Thr Ile Gln Ser Gly						
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&lt;210&gt; 5

&lt;211&gt; 12337

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

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caaactctga	gccctgattc	tgaacatgct	actttaaaga	gaatttatgg	taaatacttg	11340
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ccagctttca	cggatctaga	ggtgatcacc	aatcgcccaa	agggcttcac	caggtttcgg	11520
tcggccgtca	gagtatccat	tgcaatttcc	agaatgaaat	ttttggttcg	acggtggcat	11580
cgagtcacag	gttctgttcc	catcaatatt	aacagagatg	gctttggact	gaatcaaggt	11640

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gcagaaaaga ctgactcatt ttatcattct tctggtgggc tggagttata tggagaacca 11700
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cagaataggt acccaggcac tccagctgat ttcaatcctg gttcttttagc atgttctcag 11820
cttcagaatt acgatcctga cagagcccta acagattata tcaactcggct agaggcactg 11880
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tgcacaatga gcaccagtgt gcaaggtact ctgagtttac agagcctaac tggagaacgt 12240
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agcagagcga gaccctgtct caaagaaaaa aaaaaaaa 12337

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&lt;210&gt; 6

&lt;211&gt; 3925

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 6

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Met Glu Asp Glu Glu Arg Gln Lys Lys Leu Glu Ala Gly Lys Ala Lys
1      5      10      15
Leu Ala Gln Phe Arg Gln Arg Lys Ala Gln Ser Asp Gly Gln Ser Pro
20      25      30
Ser Lys Lys Gln Lys Lys Lys Arg Lys Thr Ser Ser Ser Lys His Asp
35      40      45
Val Ser Ala His His Asp Leu Asn Ile Asp Gln Ser Gln Cys Asn Glu
50      55      60
Met Tyr Ile Asn Ser Ser Gln Arg Val Glu Ser Thr Val Ile Pro Glu
65      70      75      80
Ser Thr Ile Met Arg Thr Leu His Ser Gly Glu Ile Thr Ser His Glu
85      90      95
Gln Gly Phe Ser Val Glu Leu Glu Ser Glu Ile Ser Thr Thr Ala Asp
100     105     110
Asp Cys Ser Ser Glu Val Asn Gly Cys Ser Phe Val Met Arg Thr Gly
115     120     125
Lys Pro Thr Asn Leu Leu Arg Glu Glu Glu Phe Gly Val Asp Asp Ser
130     135     140
Tyr Ser Glu Gln Gly Ala Gln Asp Ser Pro Thr His Leu Glu Met Met
145     150     155     160
Glu Ser Glu Leu Ala Gly Lys Gln His Glu Ile Glu Glu Leu Asn Arg
165     170     175
Glu Leu Glu Glu Met Arg Val Thr Tyr Gly Thr Glu Gly Leu Gln Gln
180     185     190
Leu Gln Glu Phe Glu Ala Ala Ile Lys Gln Arg Asp Gly Ile Ile Thr
195     200     205
Gln Leu Thr Ala Asn Leu Gln Gln Ala Arg Arg Glu Lys Asp Glu Thr
210     215     220
Met Arg Glu Phe Leu Glu Leu Thr Glu Gln Ser Gln Lys Leu Gln Ile
225     230     235     240
Gln Phe Gln Gln Leu Gln Ala Ser Glu Thr Leu Arg Asn Ser Thr His
245     250     255
Ser Ser Thr Ala Ala Asp Leu Leu Gln Ala Lys Gln Gln Ile Leu Thr
260     265     270
His Gln Gln Gln Leu Glu Glu Gln Asp His Leu Leu Glu Asp Tyr Gln
275     280     285
Lys Lys Lys Glu Asp Phe Thr Met Gln Ile Ser Phe Leu Gln Glu Lys
290     295     300
Ile Lys Val Tyr Glu Met Glu Gln Asp Lys Lys Val Glu Asn Ser Asn
305     310     315     320

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Lys Glu Glu Ile Gln Glu Lys Glu Thr Ile Ile Glu Glu Leu Asn Thr  
 325 330 335  
 Lys Ile Ile Glu Glu Glu Lys Lys Thr Leu Glu Leu Lys Asp Lys Leu  
 340 345 350  
 Thr Thr Ala Asp Lys Leu Leu Gly Glu Leu Gln Glu Gln Ile Val Gln  
 355 360 365  
 Lys Asn Gln Glu Ile Lys Asn Met Lys Leu Glu Leu Thr Asn Ser Lys  
 370 375 380  
 Gln Lys Glu Arg Gln Ser Ser Glu Glu Ile Lys Gln Leu Met Gly Thr  
 385 390 395 400  
 Val Glu Glu Leu Gln Lys Arg Asn His Lys Asp Ser Gln Phe Glu Thr  
 405 410 415  
 Asp Ile Val Gln Arg Met Glu Gln Glu Thr Gln Arg Lys Leu Glu Gln  
 420 425 430  
 Leu Arg Ala Glu Leu Asp Glu Met Tyr Gly Gln Gln Ile Val Gln Met  
 435 440 445  
 Lys Gln Glu Leu Ile Arg Gln His Met Ala Gln Met Glu Glu Met Lys  
 450 455 460  
 Thr Arg His Lys Gly Glu Met Glu Asn Ala Leu Arg Ser Tyr Ser Asn  
 465 470 475 480  
 Ile Thr Val Asn Glu Asp Gln Ile Lys Leu Met Asn Val Ala Ile Asn  
 485 490 495  
 Glu Leu Asn Ile Lys Leu Gln Asp Thr Asn Ser Gln Lys Glu Lys Leu  
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 Lys Glu Glu Leu Gly Leu Ile Leu Glu Glu Lys Cys Ala Leu Gln Arg  
 515 520 525  
 Gln Leu Glu Asp Leu Val Glu Glu Leu Ser Phe Ser Arg Glu Gln Ile  
 530 535 540  
 Gln Arg Ala Arg Gln Thr Ile Ala Glu Gln Glu Ser Lys Leu Asn Glu  
 545 550 555 560  
 Ala His Lys Ser Leu Ser Thr Val Glu Asp Leu Lys Ala Glu Ile Val  
 565 570 575  
 Ser Ala Ser Glu Ser Arg Lys Glu Leu Glu Leu Lys His Glu Ala Glu  
 580 585 590  
 Val Thr Asn Tyr Lys Ile Lys Leu Glu Met Leu Glu Lys Glu Lys Asn  
 595 600 605  
 Ala Val Leu Asp Arg Met Ala Glu Ser Gln Glu Ala Glu Leu Glu Arg  
 610 615 620  
 Leu Arg Thr Gln Leu Leu Phe Ser His Glu Glu Glu Leu Ser Lys Leu  
 625 630 635 640  
 Lys Glu Asp Leu Glu Ile Glu His Arg Ile Asn Ile Glu Lys Leu Lys  
 645 650 655  
 Asp Asn Leu Gly Ile His Tyr Lys Gln Gln Ile Asp Gly Leu Gln Asn  
 660 665 670  
 Glu Met Ser Gln Lys Ile Glu Thr Met Gln Phe Glu Lys Asp Asn Leu  
 675 680 685  
 Ile Thr Lys Gln Asn Gln Leu Ile Leu Glu Ile Ser Lys Leu Lys Asp  
 690 695 700  
 Leu Gln Gln Ser Leu Val Asn Ser Lys Ser Glu Glu Met Thr Leu Gln  
 705 710 715 720  
 Ile Asn Glu Leu Gln Lys Glu Ile Glu Ile Leu Arg Gln Glu Glu Lys  
 725 730 735  
 Glu Lys Gly Thr Leu Glu Gln Glu Val Gln Glu Leu Gln Leu Lys Thr  
 740 745 750  
 Glu Leu Leu Glu Lys Gln Met Lys Glu Lys Glu Asn Asp Leu Gln Glu  
 755 760 765  
 Lys Phe Ala Gln Leu Glu Ala Glu Asn Ser Ile Leu Lys Asp Glu Lys  
 770 775 780  
 Lys Thr Leu Glu Asp Met Leu Lys Ile His Thr Pro Val Ser Gln Glu



785					790					795					800
Glu	Arg	Leu	Ile	Phe	Leu	Asp	Ser	Ile	Lys	Ser	Lys	Ser	Lys	Asp	Ser
				805					810					815	
Val	Trp	Glu	Lys	Glu	Ile	Glu	Ile	Leu	Ile	Glu	Glu	Asn	Glu	Asp	Leu
			820					825					830		
Lys	Gln	Gln	Cys	Ile	Gln	Leu	Asn	Glu	Glu	Ile	Glu	Lys	Gln	Arg	Asn
			835				840					845			
Thr	Phe	Ser	Phe	Ala	Glu	Lys	Asn	Phe	Glu	Val	Asn	Tyr	Gln	Glu	Leu
	850					855					860				
Gln	Glu	Glu	Tyr	Ala	Cys	Leu	Leu	Lys	Val	Lys	Asp	Asp	Leu	Glu	Asp
865					870				875						880
Ser	Lys	Asn	Lys	Gln	Glu	Leu	Glu	Tyr	Lys	Ser	Lys	Leu	Lys	Ala	Leu
				885				890						895	
Asn	Glu	Glu	Leu	His	Leu	Gln	Arg	Ile	Asn	Pro	Thr	Thr	Val	Lys	Met
			900					905					910		
Lys	Ser	Ser	Val	Phe	Asp	Glu	Asp	Lys	Thr	Phe	Val	Ala	Glu	Thr	Leu
			915				920					925			
Glu	Met	Gly	Glu	Val	Val	Glu	Lys	Asp	Thr	Thr	Glu	Leu	Met	Glu	Lys
	930					935					940				
Leu	Glu	Val	Thr	Lys	Arg	Glu	Lys	Leu	Glu	Leu	Ser	Gln	Arg	Leu	Ser
945					950					955					960
Asp	Leu	Ser	Glu	Gln	Leu	Lys	Gln	Lys	His	Gly	Glu	Ile	Ser	Phe	Leu
				965					970					975	
Asn	Glu	Glu	Val	Lys	Ser	Leu	Lys	Gln	Glu	Lys	Glu	Gln	Val	Ser	Leu
			980					985					990		
Arg	Cys	Arg	Glu	Leu	Glu	Ile	Ile	Ile	Asn	His	Asn	Arg	Ala	Glu	Asn
	995						1000					1005			
Val	Gln	Ser	Cys	Asp	Thr	Gln	Val	Ser	Ser	Leu	Leu	Asp	Gly	Val	Val
	1010					1015					1020				
Thr	Met	Thr	Ser	Arg	Gly	Ala	Glu	Gly	Ser	Val	Ser	Lys	Val	Asn	Lys
1025					1030					1035					1040
Ser	Phe	Gly	Glu	Glu	Ser	Lys	Ile	Met	Val	Glu	Asp	Lys	Val	Ser	Phe
				1045					1050					1055	
Glu	Asn	Met	Thr	Val	Gly	Glu	Glu	Ser	Lys	Gln	Glu	Gln	Leu	Ile	Leu
			1060					1065					1070		
Asp	His	Leu	Pro	Ser	Val	Thr	Lys	Glu	Ser	Ser	Leu	Arg	Ala	Thr	Gln
	1075						1080					1085			
Pro	Ser	Glu	Asn	Asp	Lys	Leu	Gln	Lys	Glu	Leu	Asn	Val	Leu	Lys	Ser
	1090					1095					1100				
Glu	Gln	Asn	Asp	Leu	Arg	Leu	Gln	Met	Glu	Ala	Gln	Arg	Ile	Cys	Leu
1105					1110					1115					1120
Ser	Leu	Val	Tyr	Ser	Thr	His	Val	Asp	Gln	Val	Arg	Glu	Tyr	Met	Glu
				1125					1130					1135	
Asn	Glu	Lys	Asp	Lys	Ala	Leu	Cys	Ser	Leu	Lys	Glu	Glu	Leu	Ile	Phe
			1140					1145					1150		
Ala	Gln	Glu	Glu	Lys	Ile	Lys	Glu	Leu	Gln	Lys	Ile	His	Gln	Leu	Glu
	1155						1160					1165			
Leu	Gln	Thr	Met	Lys	Thr	Gln	Glu	Thr	Gly	Asp	Glu	Gly	Lys	Pro	Leu
	1170					1175					1180				
His	Leu	Leu	Ile	Gly	Lys	Leu	Gln	Lys	Ala	Val	Ser	Glu	Glu	Cys	Ser
1185					1190				1195						1200
Tyr	Phe	Leu	Gln	Thr	Leu	Cys	Ser	Val	Leu	Gly	Glu	Tyr	Tyr	Thr	Pro
				1205					1210					1215	
Ala	Leu	Lys	Cys	Glu	Val	Asn	Ala	Glu	Asp	Lys	Glu	Asn	Ser	Gly	Asp
			1220					1225					1230		
Tyr	Ile	Ser	Glu	Asn	Glu	Asp	Pro	Glu	Leu	Gln	Asp	Tyr	Arg	Tyr	Glu
	1235						1240					1245			
Val	Gln	Asp	Phe	Gln	Glu	Asn	Met	His	Thr	Leu	Leu	Asn	Lys	Val	Thr
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 Asn Leu Glu Asp Ile Asp Val Asn His Lys Ser Lys Leu Ser Ser Leu  
 1315 1320 1325  
 Gln Asp Leu Glu Lys Thr Lys Leu Glu Glu Gln Val Gln Glu Leu Glu  
 1330 1335 1340  
 Ser Leu Ile Ser Ser Leu Gln Gln Gln Leu Lys Glu Thr Glu Gln Asn  
 1345 1350 1355 1360  
 Tyr Glu Ala Glu Ile His Cys Leu Gln Lys Arg Leu Gln Ala Val Ser  
 1365 1370 1375  
 Glu Ser Thr Val Pro Pro Ser Leu Pro Val Asp Ser Val Val Ile Thr  
 1380 1385 1390  
 Glu Ser Asp Ala Gln Arg Thr Met Tyr Pro Gly Ser Cys Val Lys Lys  
 1395 1400 1405  
 Asn Ile Asp Gly Thr Ile Glu Phe Ser Gly Glu Phe Gly Val Lys Glu  
 1410 1415 1420  
 Glu Thr Asn Ile Val Lys Leu Leu Glu Lys Gln Tyr Gln Glu Gln Leu  
 1425 1430 1435 1440  
 Glu Glu Glu Val Ala Lys Val Ile Val Ser Met Ser Ile Ala Phe Ala  
 1445 1450 1455  
 Gln Gln Thr Glu Leu Ser Arg Ile Ser Gly Gly Lys Glu Asn Thr Ala  
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 Ser Ser Lys Gln Ala His Ala Val Cys Gln Gln Glu Gln His Tyr Phe  
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 Asn Glu Met Lys Leu Ser Gln Asp Gln Ile Gly Phe Gln Thr Phe Glu  
 1490 1495 1500  
 Thr Val Asp Val Lys Phe Lys Glu Glu Phe Lys Pro Leu Ser Lys Glu  
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 Leu Gly Glu His Gly Lys Glu Ile Leu Leu Ser Asn Ser Asp Pro His  
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 1540 1545 1550  
 Phe Ser Lys Asp Lys Thr Phe Ile Val Arg Gln Ser Ile His Asp Glu  
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 1635 1640 1645  
 Val Ser Glu Arg Glu Arg Val Leu Leu Glu Glu Leu Glu Ala Leu Lys  
 1650 1655 1660  
 Gln Leu Ser Leu Ala Gly Arg Glu Lys Leu Cys Cys Glu Leu Arg Asn  
 1665 1670 1675 1680  
 Ser Ser Thr Gln Thr Gln Asn Gly Asn Glu Asn Gln Gly Glu Val Glu  
 1685 1690 1695  
 Glu Gln Thr Phe Lys Glu Lys Glu Leu Asp Arg Lys Pro Glu Asp Val  
 1700 1705 1710  
 Pro Pro Glu Ile Leu Ser Asn Glu Arg Tyr Ala Leu Gln Lys Ala Asn  
 1715 1720 1725  
 Asn Arg Leu Leu Lys Ile Leu Leu Glu Val Val Lys Thr Thr Ala Ala

1730	1735	1740
Val Glu Glu Thr Ile Gly Arg His Val Leu Gly Ile Leu Asp Arg Ser		
1745	1750	1755
Ser Lys Ser Gln Ser Ser Ala Ser Leu Ile Trp Arg Ser Glu Ala Glu		1760
	1765	1770
Ala Ser Val Lys Ser Cys Val His Glu Glu His Thr Arg Val Thr Asp		1775
	1780	1785
Glu Ser Ile Pro Ser Tyr Ser Gly Ser Asp Met Pro Arg Asn Asp Ile		1790
	1795	1800
Asn Met Trp Ser Lys Val Thr Glu Glu Gly Thr Glu Leu Ser Gln Arg		1805
	1810	1815
Leu Val Arg Ser Gly Phe Ala Gly Thr Glu Ile Asp Pro Glu Asn Glu		1820
1825	1830	1835
Glu Leu Met Leu Asn Ile Ser Ser Arg Leu Gln Ala Ala Val Glu Lys		1840
	1845	1850
Leu Leu Glu Ala Ile Ser Glu Thr Ser Ser Gln Leu Glu His Ala Lys		1855
	1860	1865
Val Thr Gln Thr Glu Leu Met Arg Glu Ser Phe Arg Gln Lys Gln Glu		1870
	1875	1880
Ala Thr Glu Ser Leu Lys Cys Gln Glu Glu Leu Arg Glu Arg Leu His		1885
	1890	1895
Glu Glu Ser Arg Ala Arg Glu Gln Leu Ala Val Glu Leu Ser Lys Ala		1900
1905	1910	1915
Glu Gly Val Ile Asp Gly Tyr Ala Asp Glu Lys Thr Leu Phe Glu Arg		1920
	1925	1930
Gln Ile Gln Glu Lys Thr Asp Ile Ile Asp Arg Leu Glu Gln Glu Leu		1935
	1940	1945
Leu Cys Ala Ser Asn Arg Leu Gln Glu Leu Glu Ala Glu Gln Gln Gln		1950
	1955	1960
Ile Gln Glu Glu Arg Glu Leu Leu Ser Arg Gln Lys Glu Ala Met Lys		1965
	1970	1975
Ala Glu Ala Gly Pro Val Glu Gln Gln Leu Leu Gln Glu Thr Glu Lys		1980
1985	1990	1995
Leu Met Lys Glu Lys Leu Glu Val Gln Cys Gln Ala Glu Lys Val Arg		2000
	2005	2010
Asp Asp Leu Gln Lys Gln Val Lys Ala Leu Glu Ile Asp Val Glu Glu		2015
	2020	2025
Gln Val Ser Arg Phe Ile Glu Leu Glu Gln Glu Lys Asn Thr Glu Leu		2030
	2035	2040
Met Asp Leu Arg Gln Gln Asn Gln Ala Leu Glu Lys Gln Leu Glu Lys		2045
	2050	2055
Met Arg Lys Phe Leu Asp Glu Gln Ala Ile Asp Arg Glu His Glu Arg		2060
2065	2070	2075
Asp Val Phe Gln Gln Glu Ile Gln Lys Leu Glu Gln Gln Leu Lys Val		2080
	2085	2090
Val Pro Arg Phe Gln Pro Ile Ser Glu His Gln Thr Arg Glu Val Glu		2095
	2100	2105
Gln Leu Ala Asn His Leu Lys Glu Lys Thr Asp Lys Cys Ser Glu Leu		2110
	2115	2120
Leu Leu Ser Lys Glu Gln Leu Gln Arg Asp Ile Gln Glu Arg Asn Glu		2125
	2130	2135
Glu Ile Glu Lys Leu Glu Phe Arg Val Arg Glu Leu Glu Gln Ala Leu		2140
2145	2150	2155
Leu Val Ser Ala Asp Thr Phe Gln Lys Val Glu Asp Arg Lys His Phe		2160
	2165	2170
Gly Ala Val Glu Ala Lys Pro Glu Leu Ser Leu Glu Val Gln Leu Gln		2175
	2180	2185
Ala Glu Arg Asp Ala Ile Asp Arg Lys Glu Lys Glu Ile Thr Asn Leu		2190
	2195	2200
		2205

Glu Glu Gln Leu Glu Gln Phe Arg Glu Glu Leu Glu Asn Lys Asn Glu  
 2210 2215 2220  
 Glu Val Gln Gln Leu His Met Gln Leu Glu Ile Gln Lys Lys Glu Ser  
 2225 2230 2235 2240  
 Thr Thr Arg Leu Gln Glu Leu Glu Gln Glu Asn Lys Leu Phe Lys Asp  
 2245 2250 2255  
 Asp Met Glu Lys Leu Gly Leu Ala Ile Lys Glu Ser Asp Ala Met Ser  
 2260 2265 2270  
 Thr Gln Asp Gln His Val Leu Phe Gly Lys Phe Ala Gln Ile Ile Gln  
 2275 2280 2285  
 Glu Lys Glu Val Glu Ile Asp Gln Leu Asn Glu Gln Val Thr Lys Leu  
 2290 2295 2300  
 Gln Gln Gln Leu Lys Ile Thr Thr Asp Asn Lys Val Ile Glu Glu Lys  
 2305 2310 2315 2320  
 Asn Glu Leu Ile Arg Asp Leu Glu Thr Gln Ile Glu Cys Leu Met Ser  
 2325 2330 2335  
 Asp Gln Glu Cys Val Lys Arg Asn Arg Glu Glu Glu Ile Glu Gln Leu  
 2340 2345 2350  
 Asn Glu Val Ile Glu Lys Leu Gln Gln Glu Leu Ala Asn Ile Gly Gln  
 2355 2360 2365  
 Lys Thr Ser Met Asn Ala His Ser Leu Ser Glu Glu Ala Asp Ser Leu  
 2370 2375 2380  
 Lys His Gln Leu Asp Val Val Ile Ala Glu Lys Leu Ala Leu Glu Gln  
 2385 2390 2395 2400  
 Gln Val Glu Thr Ala Asn Glu Glu Met Thr Phe Met Lys Asn Val Leu  
 2405 2410 2415  
 Lys Glu Thr Asn Phe Lys Met Asn Gln Leu Thr Gln Glu Leu Phe Ser  
 2420 2425 2430  
 Leu Lys Arg Glu Arg Glu Ser Val Glu Lys Ile Gln Ser Ile Pro Glu  
 2435 2440 2445  
 Asn Ser Val Asn Val Ala Ile Asp His Leu Ser Lys Asp Lys Pro Glu  
 2450 2455 2460  
 Leu Glu Val Val Leu Thr Glu Asp Ala Leu Lys Ser Leu Glu Asn Gln  
 2465 2470 2475 2480  
 Thr Tyr Phe Lys Ser Phe Glu Glu Asn Gly Lys Gly Ser Ile Ile Asn  
 2485 2490 2495  
 Leu Glu Thr Arg Leu Leu Gln Leu Glu Ser Thr Val Ser Ala Lys Asp  
 2500 2505 2510  
 Leu Glu Leu Thr Gln Cys Tyr Lys Gln Ile Lys Asp Met Gln Glu Gln  
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 Gly Gln Phe Glu Thr Glu Met Leu Gln Lys Lys Ile Val Asn Leu Gln  
 2530 2535 2540  
 Lys Ile Val Glu Glu Lys Val Ala Ala Ala Leu Val Ser Gln Ile Gln  
 2545 2550 2555 2560  
 Leu Glu Ala Val Gln Glu Tyr Ala Lys Phe Cys Gln Asp Asn Gln Thr  
 2565 2570 2575  
 Ile Ser Ser Glu Pro Glu Arg Thr Asn Ile Gln Asn Leu Asn Gln Leu  
 2580 2585 2590  
 Arg Glu Asp Glu Leu Gly Ser Asp Ile Ser Ala Leu Thr Leu Arg Ile  
 2595 2600 2605  
 Ser Glu Leu Glu Ser Gln Val Val Glu Met His Thr Ser Leu Ile Leu  
 2610 2615 2620  
 Glu Lys Glu Gln Val Glu Ile Ala Glu Lys Asn Val Leu Glu Lys Glu  
 2625 2630 2635 2640  
 Lys Lys Leu Leu Glu Leu Gln Lys Leu Leu Glu Gly Asn Glu Lys Lys  
 2645 2650 2655  
 Gln Arg Glu Lys Glu Lys Lys Arg Ser Pro Gln Asp Val Glu Val Leu  
 2660 2665 2670  
 Lys Thr Thr Thr Glu Leu Phe His Ser Asn Glu Glu Ser Gly Phe Phe

2675	2680	2685
Asn Glu Leu Glu Ala Leu Arg Ala Glu Ser Val Ala Thr Lys Ala Glu		
2690	2695	2700
Leu Ala Ser Tyr Lys Glu Lys Ala Glu Lys Leu Gln Glu Glu Leu Leu		
2705	2710	2715
Val Lys Glu Thr Asn Met Thr Ser Leu Gln Lys Asp Leu Ser Gln Val		
	2725	2730
Arg Asp His Leu Ala Glu Ala Lys Glu Lys Leu Ser Ile Leu Glu Lys		
	2740	2745
Glu Asp Glu Thr Glu Val Gln Glu Ser Lys Lys Ala Cys Met Phe Glu		
	2755	2760
Pro Leu Pro Ile Lys Leu Ser Lys Ser Ile Ala Ser Gln Thr Asp Gly		
	2770	2775
Thr Leu Lys Ile Ser Ser Ser Asn Gln Thr Pro Gln Ile Leu Val Lys		
2785	2790	2795
Asn Ala Gly Ile Gln Ile Asn Leu Gln Ser Glu Cys Ser Ser Glu Glu		
	2805	2810
Val Thr Glu Ile Ile Ser Gln Phe Thr Glu Lys Ile Glu Lys Met Gln		
	2820	2825
Glu Leu His Ala Ala Glu Ile Leu Asp Met Glu Ser Arg His Ile Ser		
	2835	2840
Glu Thr Glu Thr Leu Lys Arg Glu His Tyr Val Ala Val Gln Leu Leu		
	2850	2855
Lys Glu Glu Cys Gly Thr Leu Lys Ala Val Ile Gln Cys Leu Arg Ser		
2865	2870	2875
Lys Glu Gly Ser Ser Ile Pro Glu Leu Ala His Ser Asp Ala Tyr Gln		
	2885	2890
Thr Arg Glu Ile Cys Ser Ser Asp Ser Gly Ser Asp Trp Gly Gln Gly		
	2900	2905
Ile Tyr Leu Thr His Ser Gln Gly Phe Asp Ile Ala Ser Glu Gly Arg		
	2915	2920
Gly Glu Glu Ser Glu Ser Ala Thr Asp Ser Phe Pro Lys Lys Ile Lys		
	2930	2935
Gly Leu Leu Arg Ala Val His Asn Glu Gly Met Gln Val Leu Ser Leu		
2945	2950	2955
Thr Glu Ser Pro Tyr Ser Asp Gly Glu Asp His Ser Ile Gln Gln Val		
	2965	2970
Ser Glu Pro Trp Leu Glu Glu Arg Lys Ala Tyr Ile Asn Thr Ile Ser		
	2980	2985
Ser Leu Lys Asp Leu Ile Thr Lys Met Gln Leu Gln Arg Glu Ala Glu		
	2995	3000
Val Tyr Asp Ser Ser Gln Ser His Glu Ser Phe Ser Asp Trp Arg Gly		
	3010	3015
Glu Leu Leu Leu Ala Leu Gln Gln Val Phe Leu Glu Glu Arg Ser Val		
3025	3030	3035
Leu Leu Ala Ala Phe Arg Thr Glu Leu Thr Ala Leu Gly Thr Thr Asp		
	3045	3050
Ala Val Gly Leu Leu Asn Cys Leu Glu Gln Arg Ile Gln Glu Gln Gly		
	3060	3065
Val Glu Tyr Gln Ala Ala Met Glu Cys Leu Gln Lys Ala Asp Arg Arg		
	3075	3080
Ser Leu Leu Ser Glu Ile Gln Ala Leu His Ala Gln Met Asn Gly Arg		
	3090	3095
Lys Ile Thr Leu Lys Arg Glu Gln Glu Ser Glu Lys Pro Ser Gln Glu		
3105	3110	3115
Leu Leu Glu Tyr Asn Ile Gln Gln Lys Gln Ser Gln Met Leu Glu Met		
	3125	3130
Gln Val Glu Leu Ser Ser Met Lys Asp Arg Ala Thr Glu Leu Gln Glu		
	3140	3145
		3150

Gln Leu Ser Ser Glu Lys Met Val Val Ala Glu Leu Lys Ser Glu Leu  
 3155 3160 3165  
 Ala Gln Thr Lys Leu Glu Leu Glu Thr Thr Leu Lys Ala Gln His Lys  
 3170 3175 3180  
 His Leu Lys Glu Leu Glu Ala Phe Arg Leu Glu Val Lys Asp Lys Thr  
 3185 3190 3195 3200  
 Asp Glu Val His Leu Leu Asn Asp Thr Leu Ala Ser Glu Gln Lys Lys  
 3205 3210 3215  
 Ser Arg Glu Leu Gln Trp Ala Leu Glu Lys Glu Lys Ala Lys Leu Gly  
 3220 3225 3230  
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cttcagcgcc	agctggaaga	gaaaagacaa	caagtttata	agttagacct	tgaaggacag	10500
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gtgtccccaa	gtacttcttg	tggtctcattg	actgaaagac	tactgagaca	aaatgctgag	10980
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ggctactctga gtttacagag cctaactgga gaacgtattc ctaagtagcg catggcagaa 12240
agtgttaagg ccgtgccgca gcantccagc ctgggcagca gagcgagacc ctgtctcaaa 12300
gaaaaaaaaa aaa 12313

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&lt;210&gt; 8

&lt;211&gt; 3917

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 8

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Met Glu Asp Glu Glu Arg Gln Lys Lys Leu Glu Ala Gly Lys Ala Lys
 1          5          10          15
Leu Ala Gln Phe Arg Gln Arg Lys Ala Gln Ser Asp Gly Gln Ser Pro
 20          25          30
Ser Lys Lys Gln Lys Lys Lys Arg Lys Thr Ser Ser Ser Lys Lys Asp
 35          40          45
Val Ser Ala His His Asp Leu Asn Ile Asp Gln Ser Gln Cys Asn Glu
 50          55          60
Met Tyr Ile Asn Ser Ser Gln Arg Val Glu Ser Thr Val Ile Pro Glu
 65          70          75          80
Ser Thr Ile Met Arg Thr Leu His Ser Gly Glu Ile Thr Ser His Glu
 85          90          95
Gln Gly Phe Ser Val Glu Leu Glu Ser Glu Ile Ser Thr Thr Ala Asp
100          105          110
Asp Cys Ser Ser Glu Val Asn Gly Cys Ser Phe Val Met Arg Thr Gly
115          120          125
Lys Pro Thr Asn Leu Leu Arg Glu Glu Glu Phe Gly Val Asp Asp Ser
130          135          140
Tyr Ser Glu Gln Gly Ala Gln Asp Ser Pro Thr His Leu Glu Met Met
145          150          155          160
Glu Ser Glu Leu Ala Gly Lys Gln His Glu Ile Glu Glu Leu Asn Arg
165          170          175
Glu Leu Glu Glu Met Arg Val Thr Tyr Gly Thr Glu Gly Leu Gln Gln
180          185          190
Leu Gln Glu Phe Glu Ala Ala Ile Lys Gln Arg Asp Gly Ile Ile Thr
195          200          205
Gln Leu Thr Ala Asn Leu Gln Gln Ala Arg Arg Glu Lys Asp Glu Thr
210          215          220
Met Arg Glu Phe Leu Glu Leu Thr Glu Gln Ser Gln Lys Leu Gln Ile
225          230          235          240

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Gln	Phe	Gln	Gln	Leu	Gln	Ala	Ser	Glu	Thr	Leu	Arg	Asn	Ser	Thr	His	245	250	255
Ser	Ser	Thr	Ala	Ala	Asp	Leu	Leu	Gln	Ala	Lys	Gln	Gln	Ile	Leu	Thr	260	265	270
His	Gln	Gln	Gln	Leu	Glu	Glu	Gln	Asp	His	Leu	Leu	Glu	Asp	Tyr	Gln	275	280	285
Lys	Lys	Lys	Glu	Asp	Phe	Thr	Met	Gln	Ile	Ser	Phe	Leu	Gln	Glu	Lys	290	295	300
Ile	Lys	Val	Tyr	Glu	Met	Glu	Gln	Asp	Lys	Lys	Val	Glu	Asn	Ser	Asn	305	310	320
Lys	Glu	Glu	Ile	Gln	Glu	Lys	Glu	Thr	Ile	Ile	Glu	Glu	Leu	Asn	Thr	325	330	335
Lys	Ile	Ile	Glu	Glu	Glu	Lys	Lys	Thr	Leu	Glu	Leu	Lys	Asp	Lys	Leu	340	345	350
Thr	Thr	Ala	Asp	Lys	Leu	Leu	Gly	Glu	Leu	Gln	Glu	Gln	Ile	Val	Gln	355	360	365
Lys	Asn	Gln	Glu	Ile	Lys	Asn	Met	Lys	Leu	Glu	Leu	Thr	Asn	Ser	Lys	370	375	380
Gln	Lys	Glu	Arg	Gln	Ser	Ser	Glu	Glu	Ile	Lys	Gln	Leu	Met	Gly	Thr	385	390	400
Val	Glu	Glu	Leu	Gln	Lys	Arg	Asn	His	Lys	Asp	Ser	Gln	Phe	Glu	Thr	405	410	415
Asp	Ile	Val	Gln	Arg	Met	Glu	Gln	Glu	Thr	Gln	Arg	Lys	Leu	Glu	Gln	420	425	430
Leu	Arg	Ala	Glu	Leu	Asp	Glu	Met	Tyr	Gly	Gln	Gln	Ile	Val	Gln	Met	435	440	445
Lys	Gln	Glu	Leu	Ile	Arg	Gln	His	Met	Ala	Gln	Met	Glu	Glu	Met	Lys	450	455	460
Thr	Arg	His	Lys	Gly	Glu	Met	Glu	Asn	Ala	Leu	Arg	Ser	Tyr	Ser	Asn	465	470	480
Ile	Thr	Val	Asn	Glu	Asp	Gln	Ile	Lys	Leu	Met	Asn	Val	Ala	Ile	Asn	485	490	495
Glu	Leu	Asn	Ile	Lys	Leu	Gln	Asp	Thr	Asn	Ser	Gln	Lys	Glu	Lys	Leu	500	505	510
Lys	Glu	Glu	Leu	Gly	Leu	Ile	Leu	Glu	Glu	Lys	Cys	Ala	Leu	Gln	Arg	515	520	525
Gln	Leu	Glu	Asp	Leu	Val	Glu	Glu	Leu	Ser	Phe	Ser	Arg	Glu	Gln	Ile	530	535	540
Gln	Arg	Ala	Arg	Gln	Thr	Ile	Ala	Glu	Gln	Glu	Ser	Lys	Leu	Asn	Glu	545	550	555
Ala	His	Lys	Ser	Leu	Ser	Thr	Val	Glu	Asp	Leu	Lys	Ala	Glu	Ile	Val	565	570	575
Ser	Ala	Ser	Glu	Ser	Arg	Lys	Glu	Leu	Glu	Leu	Lys	His	Glu	Ala	Glu	580	585	590
Val	Thr	Asn	Tyr	Lys	Ile	Lys	Leu	Glu	Met	Leu	Glu	Lys	Glu	Lys	Asn	595	600	605
Ala	Val	Leu	Asp	Arg	Met	Ala	Glu	Ser	Gln	Glu	Ala	Glu	Leu	Glu	Arg	610	615	620
Leu	Arg	Thr	Gln	Leu	Leu	Phe	Ser	His	Glu	Glu	Glu	Leu	Ser	Lys	Leu	625	630	640
Lys	Glu	Asp	Leu	Glu	Ile	Glu	His	Arg	Ile	Asn	Ile	Glu	Lys	Leu	Lys	645	650	655
Asp	Asn	Leu	Gly	Ile	His	Tyr	Lys	Gln	Gln	Ile	Asp	Gly	Leu	Gln	Asn	660	665	670
Glu	Met	Ser	Gln	Lys	Ile	Glu	Thr	Met	Gln	Phe	Glu	Lys	Asp	Asn	Leu	675	680	685
Ile	Thr	Lys	Gln	Asn	Gln	Leu	Ile	Leu	Glu	Ile	Ser	Lys	Leu	Lys	Asp	690	695	700
Leu	Gln	Gln	Ser	Leu	Val	Asn	Ser	Lys	Ser	Glu	Glu	Met	Thr	Leu	Gln			

705					710					715				720
Ile	Asn	Glu	Leu	Gln	Lys	Glu	Ile	Glu	Ile	Leu	Arg	Gln	Glu	Glu
				725					730					735
Glu	Lys	Gly	Thr	Leu	Glu	Gln	Glu	Val	Gln	Glu	Leu	Gln	Leu	Lys
			740					745					750	
Glu	Leu	Leu	Glu	Lys	Gln	Met	Lys	Glu	Lys	Glu	Asn	Asp	Leu	Gln
		755					760				765			
Lys	Phe	Ala	Gln	Leu	Glu	Ala	Glu	Asn	Ser	Ile	Leu	Lys	Asp	Glu
	770					775					780			Lys
Lys	Thr	Leu	Glu	Asp	Met	Leu	Lys	Ile	His	Thr	Pro	Val	Ser	Gln
785				790					795					800
Glu	Arg	Leu	Ile	Phe	Leu	Asp	Ser	Ile	Lys	Ser	Lys	Ser	Lys	Asp
				805					810					815
Val	Trp	Glu	Lys	Glu	Ile	Glu	Ile	Leu	Ile	Glu	Glu	Asn	Glu	Asp
			820					825					830	Leu
Lys	Gln	Gln	Cys	Ile	Gln	Leu	Asn	Glu	Glu	Ile	Glu	Lys	Gln	Arg
	835						840					845		Asn
Thr	Phe	Ser	Phe	Ala	Glu	Lys	Asn	Phe	Glu	Val	Asn	Tyr	Gln	Glu
	850					855					860			Leu
Gln	Glu	Glu	Tyr	Ala	Cys	Leu	Leu	Lys	Val	Lys	Asp	Asp	Leu	Glu
865				870					875					880
Ser	Lys	Asn	Lys	Gln	Glu	Leu	Glu	Tyr	Lys	Ser	Lys	Leu	Lys	Ala
			885						890					895
Asn	Glu	Glu	Leu	His	Leu	Gln	Arg	Ile	Asn	Pro	Thr	Thr	Val	Lys
			900					905					910	Met
Lys	Ser	Ser	Val	Phe	Asp	Glu	Asp	Lys	Thr	Phe	Val	Ala	Glu	Thr
	915						920					925		Leu
Glu	Met	Gly	Glu	Val	Val	Glu	Lys	Asp	Thr	Thr	Glu	Leu	Met	Glu
	930					935					940			Lys
Leu	Glu	Val	Thr	Lys	Arg	Glu	Lys	Leu	Glu	Leu	Ser	Gln	Arg	Leu
945					950				955					960
Asp	Leu	Ser	Glu	Gln	Leu	Lys	Gln	Lys	His	Gly	Glu	Ile	Ser	Phe
			965						970					975
Asn	Glu	Glu	Val	Lys	Ser	Leu	Lys	Gln	Glu	Lys	Glu	Gln	Val	Ser
			980					985					990	Leu
Arg	Cys	Arg	Glu	Leu	Glu	Ile	Ile	Ile	Asn	His	Asn	Arg	Ala	Glu
	995					1000						1005		Asn
Val	Gln	Ser	Cys	Asp	Thr	Gln	Val	Ser	Ser	Leu	Leu	Asp	Gly	Val
	1010					1015						1020		Val
Thr	Met	Thr	Ser	Arg	Gly	Ala	Glu	Gly	Ser	Val	Ser	Lys	Val	Asn
1025					1030					1035				Lys
Ser	Phe	Gly	Glu	Glu	Ser	Lys	Ile	Met	Val	Glu	Asp	Lys	Val	Ser
			1045						1050					Phe
Glu	Asn	Met	Thr	Val	Gly	Glu	Glu	Ser	Lys	Gln	Glu	Gln	Leu	Ile
			1060					1065					1070	Leu
Asp	His	Leu	Pro	Ser	Val	Thr	Lys	Glu	Ser	Ser	Leu	Arg	Ala	Thr
	1075						1080					1085		Gln
Pro	Ser	Glu	Asn	Asp	Lys	Leu	Gln	Lys	Glu	Leu	Asn	Val	Leu	Lys
	1090				1095						1100			Ser
Glu	Gln	Asn	Asp	Leu	Arg	Leu	Gln	Met	Glu	Ala	Gln	Arg	Ile	Cys
1105					1110					1115				Leu
Ser	Leu	Val	Tyr	Ser	Thr	His	Val	Asp	Gln	Val	Arg	Glu	Tyr	Met
			1125						1130					Glu
Asn	Glu	Lys	Asp	Lys	Ala	Leu	Cys	Ser	Leu	Lys	Glu	Glu	Leu	Ile
		1140						1145					1150	Phe
Ala	Gln	Glu	Glu	Lys	Ile	Lys	Glu	Leu	Gln	Lys	Ile	His	Gln	Leu
	1155						1160					1165		Glu
Leu	Gln	Thr	Met	Lys	Thr	Gln	Glu	Thr	Gly	Asp	Glu	Gly	Lys	Pro
	1170					1175					1180			Leu

His Leu Leu Ile Gly Lys Leu Gln Lys Ala Val Ser Glu Glu Cys Ser  
 1185 1190 1195 1200  
 Tyr Phe Leu Gln Thr Leu Cys Ser Val Leu Gly Glu Tyr Tyr Thr Pro  
 1205 1210 1215  
 Ala Leu Lys Cys Glu Val Asn Ala Glu Asp Lys Glu Asn Ser Gly Asp  
 1220 1225 1230  
 Tyr Ile Ser Glu Asn Glu Asp Pro Glu Leu Gln Asp Tyr Arg Tyr Glu  
 1235 1240 1245  
 Val Gln Asp Phe Gln Glu Asn Met His Thr Leu Leu Asn Lys Val Thr  
 1250 1255 1260  
 Glu Glu Tyr Asn Lys Leu Leu Val Leu Gln Thr Arg Leu Ser Lys Ile  
 1265 1270 1275 1280  
 Trp Gly Gln Gln Thr Asp Gly Met Lys Leu Glu Phe Gly Glu Glu Asn  
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 Leu Pro Lys Glu Thr Glu Phe Leu Ser Ile His Ser Gln Met Thr  
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 Asn Leu Glu Asp Ile Asp Val Asn His Lys Ser Lys Leu Ser Ser Leu  
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 Gln Asp Leu Glu Lys Thr Lys Leu Glu Glu Gln Val Gln Glu Leu Glu  
 1330 1335 1340  
 Ser Leu Ile Ser Ser Leu Gln Gln Gln Leu Lys Glu Thr Glu Gln Asn  
 1345 1350 1355 1360  
 Tyr Glu Ala Glu Ile His Cys Leu Gln Lys Arg Leu Gln Ala Val Ser  
 1365 1370 1375  
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 1395 1400 1405  
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 Glu Glu Glu Val Ala Lys Val Ile Val Ser Met Ser Ile Ala Phe Ala  
 1445 1450 1455  
 Gln Gln Thr Glu Leu Ser Arg Ile Ser Gly Gly Lys Glu Asn Thr Ala  
 1460 1465 1470  
 Ser Ser Lys Gln Ala His Ala Val Cys Gln Gln Glu Gln His Tyr Phe  
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 Asn Glu Met Lys Leu Ser Gln Asp Gln Ile Gly Phe Gln Thr Phe Glu  
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 Thr Val Asp Val Lys Phe Lys Glu Glu Phe Lys Pro Leu Ser Lys Glu  
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 Asp Ile Pro Glu Ser Lys Asp Cys Val Leu Thr Ile Ser Glu Glu Met  
 1540 1545 1550  
 Phe Ser Lys Asp Lys Thr Phe Ile Val Arg Gln Ser Ile His Asp Glu  
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 Glu Gln Leu Glu Asp Met Arg Gln Glu Leu Val Arg Gln Tyr Gln Glu  
 1585 1590 1595 1600  
 His Gln Gln Ala Thr Glu Leu Leu Arg Gln Ala His Met Arg Gln Met  
 1605 1610 1615  
 Glu Arg Gln Arg Glu Asp Gln Glu Gln Leu Gln Glu Ile Lys Arg  
 1620 1625 1630  
 Leu Asn Arg Gln Leu Ala Gln Arg Ser Ser Ile Asp Asn Glu Asn Leu  
 1635 1640 1645  
 Val Ser Glu Arg Glu Arg Val Leu Leu Glu Glu Leu Glu Ala Leu Lys

1650	1655	1660
Gln Leu Ser Leu Ala	Gly Arg Glu Lys Leu Cys Cys Glu Leu Arg Asn	
1665	1670	1675
Ser Ser Thr Gln Thr	Gln Asn Gly Asn Glu Asn Gln Gly Glu Val Glu	1680
	1685	1690
Glu Gln Thr Phe Lys	Glu Lys Glu Leu Asp Arg Lys Pro Glu Asp Val	1695
	1700	1705
Pro Pro Glu Ile Leu	Ser Asn Glu Arg Tyr Ala Leu Gln Lys Ala Asn	1710
	1715	1720
Asn Arg Leu Leu Lys	Ile Leu Leu Glu Val Val Lys Thr Thr Ala Ala	1725
	1730	1735
Val Glu Glu Thr Ile	Gly Arg His Val Leu Gly Ile Leu Asp Arg Ser	1740
1745	1750	1755
Ser Lys Ser Gln Ser	Ser Ala Ser Leu Ile Trp Arg Ser Glu Ala Glu	1760
	1765	1770
Ala Ser Val Lys Ser	Cys Val His Glu Glu His Thr Arg Val Thr Asp	1775
	1780	1785
Glu Ser Ile Pro Ser	Tyr Ser Gly Ser Asp Met Pro Arg Asn Asp Ile	1790
	1795	1800
Asn Met Trp Ser Lys	Val Thr Glu Glu Gly Thr Glu Leu Ser Gln Arg	1805
	1810	1815
Leu Val Arg Ser Gly	Phe Ala Gly Thr Glu Ile Asp Pro Glu Asn Glu	1820
1825	1830	1835
Glu Leu Met Leu Asn	Ile Ser Ser Arg Leu Gln Ala Ala Val Glu Lys	1840
	1845	1850
Leu Leu Glu Ala Ile	Ser Glu Thr Ser Ser Gln Leu Glu His Ala Lys	1855
	1860	1865
Val Thr Gln Thr Glu	Leu Met Arg Glu Ser Phe Arg Gln Lys Gln Glu	1870
	1875	1880
Ala Thr Glu Ser Leu	Lys Cys Gln Glu Glu Leu Arg Glu Arg Leu His	1885
	1890	1895
Glu Glu Ser Arg Ala	Arg Glu Gln Leu Ala Val Glu Leu Ser Lys Ala	1900
1905	1910	1915
Glu Gly Val Ile Asp	Gly Tyr Ala Asp Glu Lys Thr Leu Phe Glu Arg	1920
	1925	1930
Gln Ile Gln Glu Lys	Thr Asp Ile Ile Asp Arg Leu Glu Gln Glu Leu	1935
	1940	1945
Leu Cys Ala Ser Asn	Arg Leu Gln Glu Leu Glu Ala Glu Gln Gln Gln	1950
	1955	1960
Ile Gln Glu Glu Arg	Glu Leu Ser Arg Gln Lys Glu Ala Met Lys	1965
	1970	1975
Ala Glu Ala Gly Pro	Val Glu Gln Gln Leu Leu Gln Glu Thr Glu Lys	1980
1985	1990	1995
Leu Met Lys Glu Lys	Leu Glu Val Gln Cys Gln Ala Glu Lys Val Arg	2000
	2005	2010
Asp Asp Leu Gln Lys	Gln Val Lys Ala Leu Glu Ile Asp Val Glu Glu	2015
	2020	2025
Gln Val Ser Arg Phe	Ile Glu Leu Glu Gln Glu Lys Asn Thr Glu Leu	2030
	2035	2040
Met Asp Leu Arg Gln	Gln Asn Gln Ala Leu Glu Lys Gln Leu Glu Lys	2045
	2050	2055
Met Arg Lys Phe Leu	Asp Glu Gln Ala Ile Asp Arg Glu His Glu Arg	2060
2065	2070	2075
Asp Val Phe Gln Gln	Glu Ile Gln Lys Leu Glu Gln Gln Leu Lys Val	2080
	2085	2090
Val Pro Arg Phe Gln	Pro Ile Ser Glu His Gln Thr Arg Glu Val Glu	2095
	2100	2105
Gln Leu Ala Asn His	Leu Lys Glu Lys Thr Asp Lys Cys Ser Glu Leu	2110
	2115	2120
		2125

Leu Leu Ser Lys Glu Gln Leu Gln Arg Asp Ile Gln Glu Arg Asn Glu  
 2130 2135 2140  
 Glu Ile Glu Lys Leu Glu Phe Arg Val Arg Glu Leu Glu Gln Ala Leu  
 2145 2150 2155 2160  
 Leu Val Glu Asp Arg Lys His Phe Gly Ala Val Glu Ala Lys Pro Glu  
 2165 2170 2175  
 Leu Ser Leu Glu Val Gln Leu Gln Ala Glu Arg Asp Ala Ile Asp Arg  
 2180 2185 2190  
 Lys Glu Lys Glu Ile Thr Asn Leu Glu Glu Gln Leu Glu Gln Phe Arg  
 2195 2200 2205  
 Glu Glu Leu Glu Asn Lys Asn Glu Glu Val Gln Gln Leu His Met Gln  
 2210 2215 2220  
 Leu Glu Ile Gln Lys Lys Glu Ser Thr Thr Arg Leu Gln Glu Leu Glu  
 2225 2230 2235 2240  
 Gln Glu Asn Lys Leu Phe Lys Asp Asp Met Glu Lys Leu Gly Leu Ala  
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 Ile Lys Glu Ser Asp Ala Met Ser Thr Gln Asp Gln His Val Leu Phe  
 2260 2265 2270  
 Gly Lys Phe Ala Gln Ile Ile Gln Glu Lys Glu Val Glu Ile Asp Gln  
 2275 2280 2285  
 Leu Asn Glu Gln Val Thr Lys Leu Gln Gln Gln Leu Lys Ile Thr Thr  
 2290 2295 2300  
 Asp Asn Lys Val Ile Glu Glu Lys Asn Glu Leu Ile Arg Asp Leu Glu  
 2305 2310 2315 2320  
 Thr Gln Ile Glu Cys Leu Met Ser Asp Gln Glu Cys Val Lys Arg Asn  
 2325 2330 2335  
 Arg Glu Glu Glu Ile Glu Gln Leu Asn Glu Val Ile Glu Lys Leu Gln  
 2340 2345 2350  
 Gln Glu Leu Ala Asn Ile Gly Gln Lys Thr Ser Met Asn Ala His Ser  
 2355 2360 2365  
 Leu Ser Glu Glu Ala Asp Ser Leu Lys His Gln Leu Asp Val Val Ile  
 2370 2375 2380  
 Ala Glu Lys Leu Ala Leu Glu Gln Gln Val Glu Thr Ala Asn Glu Glu  
 2385 2390 2395 2400  
 Met Thr Phe Met Lys Asn Val Leu Lys Glu Thr Asn Phe Lys Met Asn  
 2405 2410 2415  
 Gln Leu Thr Gln Glu Leu Phe Ser Leu Lys Arg Glu Arg Glu Ser Val  
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 Glu Lys Ile Gln Ser Ile Pro Glu Asn Ser Val Asn Val Ala Ile Asp  
 2435 2440 2445  
 His Leu Ser Lys Asp Lys Pro Glu Leu Glu Val Val Leu Thr Glu Asp  
 2450 2455 2460  
 Ala Leu Lys Ser Leu Glu Asn Gln Thr Tyr Phe Lys Ser Phe Glu Glu  
 2465 2470 2475 2480  
 Asn Gly Lys Gly Ser Ile Ile Asn Leu Glu Thr Arg Leu Leu Gln Leu  
 2485 2490 2495  
 Glu Ser Thr Val Ser Ala Lys Asp Leu Glu Leu Thr Gln Cys Tyr Lys  
 2500 2505 2510  
 Gln Ile Lys Asp Met Gln Glu Gln Gly Gln Phe Glu Thr Glu Met Leu  
 2515 2520 2525  
 Gln Lys Lys Ile Val Asn Leu Gln Lys Ile Val Glu Glu Lys Val Ala  
 2530 2535 2540  
 Ala Ala Leu Val Ser Gln Ile Gln Leu Glu Ala Val Gln Glu Tyr Ala  
 2545 2550 2555 2560  
 Lys Phe Cys Gln Asp Asn Gln Thr Ile Ser Ser Glu Pro Glu Arg Thr  
 2565 2570 2575  
 Asn Ile Gln Asn Leu Asn Gln Leu Arg Glu Asp Glu Leu Gly Ser Asp  
 2580 2585 2590  
 Ile Ser Ala Leu Thr Leu Arg Ile Ser Glu Leu Glu Ser Gln Val Val



2595	2600	2605
Glu Met His Thr Ser Leu Ile Leu Glu Lys Glu Gln Val Glu Ile Ala		
2610	2615	2620
Glu Lys Asn Val Leu Glu Lys Glu Lys Lys Leu Leu Glu Leu Gln Lys		
2625	2630	2635
Leu Leu Glu Gly Asn Glu Lys Lys Gln Arg Glu Lys Glu Lys Lys Arg		
	2645	2650
Ser Pro Gln Asp Val Glu Val Leu Lys Thr Thr Thr Glu Leu Phe His		
	2660	2665
Ser Asn Glu Glu Ser Gly Phe Phe Asn Glu Leu Glu Ala Leu Arg Ala		
	2675	2680
Glu Ser Val Ala Thr Lys Ala Glu Leu Ala Ser Tyr Lys Glu Lys Ala		
	2690	2695
Glu Lys Leu Gln Glu Glu Leu Leu Val Lys Glu Thr Asn Met Thr Ser		
2705	2710	2715
Leu Gln Lys Asp Leu Ser Gln Val Arg Asp His Leu Ala Glu Ala Lys		
	2725	2730
Glu Lys Leu Ser Ile Leu Glu Lys Glu Asp Glu Thr Glu Val Gln Glu		
	2740	2745
Ser Lys Lys Ala Cys Met Phe Glu Pro Leu Pro Ile Lys Leu Ser Lys		
	2755	2760
Ser Ile Ala Ser Gln Thr Asp Gly Thr Leu Lys Ile Ser Ser Ser Asn		
	2770	2775
Gln Thr Pro Gln Ile Leu Val Lys Asn Ala Gly Ile Gln Ile Asn Leu		
2785	2790	2795
Gln Ser Glu Cys Ser Ser Glu Glu Val Thr Glu Ile Ile Ser Gln Phe		
	2805	2810
Thr Glu Lys Ile Glu Lys Met Gln Glu Leu His Ala Ala Glu Ile Leu		
	2820	2825
Asp Met Glu Ser Arg His Ile Ser Glu Thr Glu Thr Leu Lys Arg Glu		
	2835	2840
His Tyr Val Ala Val Gln Leu Leu Lys Glu Glu Cys Gly Thr Leu Lys		
	2850	2855
Ala Val Ile Gln Cys Leu Arg Ser Lys Glu Gly Ser Ser Ile Pro Glu		
2865	2870	2875
Leu Ala His Ser Asp Ala Tyr Gln Thr Arg Glu Ile Cys Ser Ser Asp		
	2885	2890
Ser Gly Ser Asp Trp Gly Gln Gly Ile Tyr Leu Thr His Ser Gln Gly		
	2900	2905
Phe Asp Ile Ala Ser Glu Gly Arg Gly Glu Glu Ser Glu Ser Ala Thr		
	2915	2920
Asp Ser Phe Pro Lys Lys Ile Lys Gly Leu Leu Arg Ala Val His Asn		
	2930	2935
Glu Gly Met Gln Val Leu Ser Leu Thr Glu Ser Pro Tyr Ser Asp Gly		
2945	2950	2955
Glu Asp His Ser Ile Gln Gln Val Ser Glu Pro Trp Leu Glu Glu Arg		
	2965	2970
Lys Ala Tyr Ile Asn Thr Ile Ser Ser Leu Lys Asp Leu Ile Thr Lys		
	2980	2985
Met Gln Leu Gln Arg Glu Ala Glu Val Tyr Asp Ser Ser Gln Ser His		
	2995	3000
Glu Ser Phe Ser Asp Trp Arg Gly Glu Leu Leu Leu Ala Leu Gln Gln		
	3010	3015
Val Phe Leu Glu Glu Arg Ser Val Leu Leu Ala Ala Phe Arg Thr Glu		
3025	3030	3035
Leu Thr Ala Leu Gly Thr Thr Asp Ala Val Gly Leu Leu Asn Cys Leu		
	3045	3050
Glu Gln Arg Ile Gln Glu Gln Gly Val Glu Tyr Gln Ala Ala Met Glu		
	3060	3065
		3070

Cys Leu Gln Lys Ala Asp Arg Arg Ser Leu Leu Ser Glu Ile Gln Ala  
 3075 3080 3085  
 Leu His Ala Gln Met Asn Gly Arg Lys Ile Thr Leu Lys Arg Glu Gln  
 3090 3095 3100  
 Glu Ser Glu Lys Pro Ser Gln Glu Leu Leu Glu Tyr Asn Ile Gln Gln  
 3105 3110 3115 3120  
 Lys Gln Ser Gln Met Leu Glu Met Gln Val Glu Leu Ser Ser Met Lys  
 3125 3130 3135  
 Asp Arg Ala Thr Glu Leu Gln Glu Gln Leu Ser Ser Glu Lys Met Val  
 3140 3145 3150  
 Val Ala Glu Leu Lys Ser Glu Leu Ala Gln Thr Lys Leu Glu Leu Glu  
 3155 3160 3165  
 Thr Thr Leu Lys Ala Gln His Lys His Leu Lys Glu Leu Glu Ala Phe  
 3170 3175 3180  
 Arg Leu Glu Val Lys Asp Lys Thr Asp Glu Val His Leu Leu Asn Asp  
 3185 3190 3195 3200  
 Thr Leu Ala Ser Glu Gln Lys Lys Ser Arg Glu Leu Gln Trp Ala Leu  
 3205 3210 3215  
 Glu Lys Glu Lys Ala Lys Leu Gly Arg Ser Glu Glu Arg Asp Lys Glu  
 3220 3225 3230  
 Glu Leu Glu Asp Leu Lys Phe Ser Leu Glu Ser Gln Lys Gln Arg Asn  
 3235 3240 3245  
 Leu Gln Leu Asn Leu Leu Leu Glu Gln Gln Lys Gln Leu Leu Asn Glu  
 3250 3255 3260  
 Ser Gln Gln Lys Ile Glu Ser Gln Arg Met Leu Tyr Asp Ala Gln Leu  
 3265 3270 3275 3280  
 Ser Glu Glu Gln Gly Arg Asn Leu Glu Leu Gln Val Leu Leu Glu Ser  
 3285 3290 3295  
 Glu Lys Val Arg Ile Arg Glu Met Ser Ser Thr Leu Asp Arg Glu Arg  
 3300 3305 3310  
 Glu Leu His Ala Gln Leu Gln Ser Ser Asp Gly Thr Gly Gln Ser Arg  
 3315 3320 3325  
 Pro Pro Leu Pro Ser Glu Asp Leu Leu Lys Glu Leu Gln Lys Gln Leu  
 3330 3335 3340  
 Glu Glu Lys His Ser Arg Ile Val Glu Leu Leu Asn Glu Thr Glu Lys  
 3345 3350 3355 3360  
 Tyr Lys Leu Asp Ser Leu Gln Thr Arg Gln Gln Met Glu Lys Asp Arg  
 3365 3370 3375  
 Gln Val His Arg Lys Thr Leu Gln Thr Glu Gln Glu Ala Asn Thr Glu  
 3380 3385 3390  
 Gly Gln Lys Lys Met His Glu Leu Gln Ser Lys Val Glu Asp Leu Gln  
 3395 3400 3405  
 Arg Gln Leu Glu Glu Lys Arg Gln Gln Val Tyr Lys Leu Asp Leu Glu  
 3410 3415 3420  
 Gly Gln Arg Leu Gln Gly Ile Met Gln Glu Phe Gln Lys Gln Glu Leu  
 3425 3430 3435 3440  
 Glu Arg Glu Glu Lys Arg Glu Ser Arg Arg Ile Leu Tyr Gln Asn Leu  
 3445 3450 3455  
 Asn Glu Pro Thr Thr Trp Ser Leu Thr Ser Asp Arg Thr Arg Asn Trp  
 3460 3465 3470  
 Val Leu Gln Gln Lys Ile Glu Gly Glu Thr Lys Glu Ser Asn Tyr Ala  
 3475 3480 3485  
 Lys Leu Ile Glu Met Asn Gly Gly Gly Thr Gly Cys Asn His Glu Leu  
 3490 3495 3500  
 Glu Met Ile Arg Gln Lys Leu Gln Cys Val Ala Ser Lys Leu Gln Val  
 3505 3510 3515 3520  
 Leu Pro Gln Lys Ala Ser Glu Arg Leu Gln Phe Glu Thr Ala Asp Asp  
 3525 3530 3535  
 Glu Asp Phe Ile Trp Val Gln Glu Asn Ile Asp Glu Ile Ile Leu Gln

3540	3545	3550
Leu Gln Lys Leu Thr Gly Gln Gln Gly Glu Glu Pro Ser Leu Val Ser		
3555	3560	3565
Pro Ser Thr Ser Cys Gly Ser Leu Thr Glu Arg Leu Leu Arg Gln Asn		
3570	3575	3580
Ala Glu Leu Thr Gly His Ile Ser Gln Leu Thr Glu Glu Lys Asn Asp		
3585	3590	3595
Leu Arg Asn Met Val Met Lys Leu Glu Glu Gln Ile Arg Trp Tyr Arg		
3605	3610	3615
Gln Thr Gly Ala Gly Arg Asp Asn Ser Ser Arg Phe Ser Leu Asn Gly		
3620	3625	3630
Gly Ala Asn Ile Glu Ala Ile Ile Ala Ser Glu Lys Glu Val Trp Asn		
3635	3640	3645
Arg Glu Lys Leu Thr Leu Gln Lys Ser Leu Lys Arg Ala Glu Ala Glu		
3650	3655	3660
Val Tyr Lys Leu Lys Ala Glu Leu Arg Asn Asp Ser Leu Leu Gln Thr		
3665	3670	3675
Leu Ser Pro Asp Ser Glu His Val Thr Leu Lys Arg Ile Tyr Gly Lys		
3685	3690	3695
Tyr Leu Arg Ala Glu Ser Phe Arg Lys Ala Leu Ile Tyr Gln Lys Lys		
3700	3705	3710
Tyr Leu Leu Leu Leu Leu Gly Gly Phe Gln Glu Cys Glu Asp Ala Thr		
3715	3720	3725
Leu Ala Leu Leu Ala Arg Met Gly Gly Gln Pro Ala Phe Thr Asp Leu		
3730	3735	3740
Glu Val Ile Thr Asn Arg Pro Lys Gly Phe Thr Arg Phe Arg Ser Ala		
3745	3750	3755
Val Arg Val Ser Ile Ala Ile Ser Arg Met Lys Phe Leu Val Arg Arg		
3765	3770	3775
Trp His Arg Val Thr Gly Ser Val Ser Ile Asn Ile Asn Arg Asp Gly		
3780	3785	3790
Phe Gly Leu Asn Gln Gly Ala Glu Lys Thr Asp Ser Phe Tyr His Ser		
3795	3800	3805
Ser Gly Gly Leu Glu Leu Tyr Gly Glu Pro Arg His Thr Thr Tyr Arg		
3810	3815	3820
Ser Arg Ser Asp Leu Asp Tyr Ile Arg Ser Pro Leu Pro Phe Gln Asn		
3825	3830	3835
Arg Tyr Pro Gly Thr Pro Ala Asp Phe Asn Pro Gly Ser Leu Ala Cys		
3845	3850	3855
Ser Gln Leu Gln Asn Tyr Asp Pro Asp Arg Ala Leu Thr Asp Tyr Ile		
3860	3865	3870
Thr Arg Leu Glu Ala Leu Gln Arg Arg Leu Gly Thr Ile Gln Ser Gly		
3875	3880	3885
Ala Leu Ser Leu Thr Thr Ser Trp Gln His His Ser Ala Arg Pro Thr		
3890	3895	3900
Ala Pro Leu Phe Phe Glu Ile Leu Ser His Ser Leu Gly		
3905	3910	3915

&lt;210&gt; 9

&lt;211&gt; 2850

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 9

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gttgtgactt tccctttcga attcctcggt atatcttggg gactggagga cctgtctggt 60
tattatacag acgcataact ggaggtggga tccacacagc tcagaacagc tggatcttgc 120
tcagtctctg ccaggggaag attccttgga ggaggccctg cagcgacatg gagggagctg 180
ctttgctgag agtctctgtc ctctgcatct ggatgagtgc acttttcctt ggtgtgagag 240

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tgaggggcaga ggaagctgga gcgaggggtgc aacaaaacgt tccaagtggg acagatactg 300
gagatcctca aagtaagccc ctcggtgact gggctgctgg caccatggac ccagagagca 360
gtatctttat tgaggatgcc attaatgtatt tcaaggaaaa agtgagcaca cagaatctgc 420
tactcctgct gactgataat gaggcctgga acggattcgt ggotgctgct gaactgccc 480
ggaatgagggc agatgagctc cgtaaagctc tggacaacct tgcaagacaa atgatcatga 540
aagacaaaaa ctggcacgat aaaggccaagc agtacagaaa ctggtttctg aaagagtttc 600
ctcggttgaa aagtaagctt gaggataaca taagaaggct ccgtgccctt gcagatgggg 660
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ccaccaggag agatatgcct ggcaggggcc aggacaaaat gcaaactttt ttttttttct 1440
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gcttgaagga accagcaatg agaaggccag gaaagaaaag agctgaaaat ggagaaagcc 2340
caagagttag aacagttgga tacaggagaa gaaacagcgg ctccactaca gaccagccc 2400
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aacagtccca tcgctcttac ccgtaagta aacagtcaga aaattagcat gaaagcagtt 2760
tagcattggg aggaagctca gatctctaga gctgtcttgt cgccgccag gattgacctg 2820
tgtgtaagtc ccaataaact cacctactca 2850

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&lt;210&gt; 10

&lt;211&gt; 383

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 10

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Met Ser Ala Leu Phe Leu Gly Val Arg Val Arg Ala Glu Glu Ala Gly
1           5           10           15
Ala Arg Val Gln Asn Val Pro Ser Gly Thr Asp Thr Gly Asp Pro
20           25           30
Gln Ser Lys Pro Leu Gly Asp Trp Ala Ala Gly Thr Met Asp Pro Glu
35           40           45
Ser Ser Ile Phe Ile Glu Asp Ala Ile Lys Tyr Phe Lys Glu Lys Val
50           55           60

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Ser Thr Gln Asn Leu Leu Leu Leu Leu Thr Asp Asn Glu Ala Trp Asn  
 65 70 75 80  
 Gly Phe Val Ala Ala Glu Leu Pro Arg Asn Glu Ala Asp Glu Leu  
 85 90 95  
 Arg Lys Ala Leu Asp Asn Leu Ala Arg Gln Met Ile Met Lys Asp Lys  
 100 105 110  
 Asn Trp His Asp Lys Gly Gln Gln Tyr Arg Asn Trp Phe Leu Lys Glu  
 115 120 125  
 Phe Pro Arg Leu Lys Ser Lys Leu Glu Asp Asn Ile Arg Arg Leu Arg  
 130 135 140  
 Ala Leu Ala Asp Gly Val Gln Lys Val His Lys Gly Thr Thr Ile Ala  
 145 150 155 160  
 Asn Val Val Ser Gly Ser Leu Ser Ile Ser Ser Gly Ile Leu Thr Leu  
 165 170 175  
 Val Gly Met Gly Leu Ala Pro Phe Thr Glu Gly Gly Ser Leu Val Leu  
 180 185 190  
 Leu Glu Pro Gly Met Glu Leu Gly Ile Thr Ala Ala Leu Thr Gly Ile  
 195 200 205  
 Thr Ser Ser Thr Ile Asp Tyr Gly Lys Lys Trp Trp Thr Gln Ala Gln  
 210 215 220  
 Ala His Asp Leu Val Ile Lys Ser Leu Asp Lys Leu Lys Glu Val Lys  
 225 230 235 240  
 Glu Phe Leu Gly Glu Asn Ile Ser Asn Phe Leu Ser Leu Ala Gly Asn  
 245 250 255  
 Thr Tyr Gln Leu Thr Arg Gly Ile Gly Lys Asp Ile Arg Ala Leu Arg  
 260 265 270  
 Arg Ala Arg Ala Asn Leu Gln Ser Val Pro His Ala Ser Ala Ser Arg  
 275 280 285  
 Pro Arg Val Thr Glu Pro Ile Ser Ala Glu Ser Gly Glu Gln Val Glu  
 290 295 300  
 Arg Val Asn Glu Pro Ser Ile Leu Glu Met Ser Arg Gly Val Lys Leu  
 305 310 315 320  
 Thr Asp Val Ala Pro Val Ser Phe Phe Leu Val Leu Asp Val Val Tyr  
 325 330 335  
 Leu Val Tyr Glu Ser Lys His Leu His Glu Gly Ala Lys Ser Glu Thr  
 340 345 350  
 Ala Glu Glu Leu Lys Lys Val Ala Gln Glu Leu Glu Glu Lys Leu Asn  
 355 360 365  
 Ile Leu Asn Asn Asn Tyr Lys Ile Leu Gln Ala Asp Gln Glu Leu  
 370 375 380

&lt;210&gt; 11

&lt;211&gt; 3004

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 11

gttgtgactt tccctttcga attcctcggt atatcttggg gactggagga cctgtctggt 60  
 tattatacag acgcataact ggaggtggga tccacacagc tcagaacagc tggatcttgc 120  
 tcagtctctg ccaggggaag attccttgac ttctggggtg atggagaaga aacaggctgt 180  
 gctgtgtccc taatgggaaa cgtggctgag acaggggagt gagaagggtg cggtgaagaa 240  
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 atctggatga gtgcactttt ccttggtgtg agagtgaggg cagaggaagc tggagcgagg 420  
 gtgcaacaaa acgttccaag tgggacagat actggagatc ctcaaagtaa gcccctcggg 480  
 gactgggctg ctggcaccat ggaccagag agcagtatct ttattgagga tgccattaag 540  
 tattttcaagg aaaaagtgag cacacagaat ctgctactcc tgctgactga taatgaggcc 600  
 tggaacggat tcgtggctgc tgctgaactg cccaggaatg aggcagatga gctccgtaaa 660

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gctctggaca accttgcaag acaaatgac atgaaagaca aaaactggca cgataaaggc 720
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aacataagaa ggctccgtgc ccttgacagat ggggttcaga aggtccacaa aggcaccacc 840
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tatggaactg agtggttagg actttggcat ttccatagct gagcacagca ggggaggggt 1980
taatgcagat ggcagtgcag caaggagaag gcaggaaacat tggagcctgc aataaggga 2040
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ctca 3004

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&lt;210&gt; 12

&lt;211&gt; 414

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 12

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Met Arg Phe Lys Ser His Thr Val Glu Leu Arg Arg Pro Cys Ser Asp
1          5          10          15
Met Glu Gly Ala Ala Leu Leu Arg Val Ser Val Leu Cys Ile Trp Met
20          25          30
Ser Ala Leu Phe Leu Gly Val Arg Val Arg Ala Glu Glu Ala Gly Ala
35          40          45
Arg Val Gln Gln Asn Val Pro Ser Gly Thr Asp Thr Gly Asp Pro Gln
50          55          60
Ser Lys Pro Leu Gly Asp Trp Ala Ala Gly Thr Met Asp Pro Glu Ser
65          70          75          80
Ser Ile Phe Ile Glu Asp Ala Ile Lys Tyr Phe Lys Glu Lys Val Ser
85          90          95

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Thr Gln Asn Leu Leu Leu Leu Thr Asp Asn Glu Ala Trp Asn Gly  
 100 105 110  
 Phe Val Ala Ala Glu Leu Pro Arg Asn Glu Ala Asp Glu Leu Arg  
 115 120 125  
 Lys Ala Leu Asp Asn Leu Ala Arg Gln Met Ile Met Lys Asp Lys Asn  
 130 135 140  
 Trp His Asp Lys Gly Gln Gln Tyr Arg Asn Trp Phe Leu Lys Glu Phe  
 145 150 155 160  
 Pro Arg Leu Lys Ser Lys Leu Glu Asp Asn Ile Arg Arg Leu Arg Ala  
 165 170 175  
 Leu Ala Asp Gly Val Gln Lys Val His Lys Gly Thr Thr Ile Ala Asn  
 180 185 190  
 Val Val Ser Gly Ser Leu Ser Ile Ser Ser Gly Ile Leu Thr Leu Val  
 195 200 205  
 Gly Met Gly Leu Ala Pro Phe Thr Glu Gly Gly Ser Leu Val Leu Leu  
 210 215 220  
 Glu Pro Gly Met Glu Leu Gly Ile Thr Ala Ala Leu Thr Gly Ile Thr  
 225 230 235 240  
 Ser Ser Thr Ile Asp Tyr Gly Lys Lys Trp Trp Thr Gln Ala Gln Ala  
 245 250 255  
 His Asp Leu Val Ile Lys Ser Leu Asp Lys Leu Lys Glu Val Lys Glu  
 260 265 270  
 Phe Leu Gly Glu Asn Ile Ser Asn Phe Leu Ser Leu Ala Gly Asn Thr  
 275 280 285  
 Tyr Gln Leu Thr Arg Gly Ile Gly Lys Asp Ile Arg Ala Leu Arg Arg  
 290 295 300  
 Ala Arg Ala Asn Leu Gln Ser Val Pro His Ala Ser Ala Ser Arg Pro  
 305 310 315 320  
 Arg Val Thr Glu Pro Ile Ser Ala Glu Ser Gly Glu Gln Val Glu Arg  
 325 330 335  
 Val Asn Glu Pro Ser Ile Leu Glu Met Ser Arg Gly Val Lys Leu Thr  
 340 345 350  
 Asp Val Ala Pro Val Ser Phe Phe Leu Val Leu Asp Val Val Tyr Leu  
 355 360 365  
 Val Tyr Glu Ser Lys His Leu His Glu Gly Ala Lys Ser Glu Thr Ala  
 370 375 380  
 Glu Glu Leu Lys Lys Val Ala Gln Glu Leu Glu Glu Lys Leu Asn Ile  
 385 390 395 400  
 Leu Asn Asn Asn Tyr Lys Ile Leu Gln Ala Asp Gln Glu Leu  
 405 410

&lt;210&gt; 13

&lt;211&gt; 2298

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 13

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 ggtgtgagag tgagggcaga gggagctgga gcaagtagaa tttctctaaa taccagctgg 180  
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&lt;210&gt; 14

&lt;211&gt; 331

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 14

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Glu Ala Trp Lys Arg Phe Val Thr Ala Ala Glu Leu Pro Arg Asp Glu
35        40        45
Ala Asp Ala Leu Tyr Glu Ala Leu Lys Lys Leu Arg Thr Tyr Ala Ala
50        55        60
Ile Glu Asp Glu Tyr Val Gln Gln Lys Asp Glu Gln Phe Arg Glu Trp
65        70        75        80
Phe Leu Lys Glu Phe Pro Gln Val Lys Arg Lys Ile Gln Glu Ser Ile
85        90        95
Glu Lys Leu Arg Ala Leu Ala Asn Gly Ile Glu Glu Val His Arg Gly
100       105       110
Cys Thr Ile Ser Asn Val Val Ser Ser Ser Thr Gly Ala Ala Ser Gly
115       120       125
Ile Met Ser Leu Ala Gly Leu Val Leu Ala Pro Phe Thr Ala Gly Thr
130       135       140
Ser Leu Ala Leu Thr Ala Ala Gly Val Gly Leu Gly Ala Ala Ser Ala
145       150       155       160
Val Thr Gly Ile Thr Ser Ile Val Glu His Ser Tyr Thr Ser Ser
165       170       175
Ala Glu Ala Glu Ala Ser Arg Leu Thr Ala Thr Ser Ile Asp Arg Leu
180       185       190

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Lys	Val	Phe	Lys	Glu	Val	Met	Arg	Asp	Ile	Thr	Pro	Asn	Leu	Leu	Ser
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	210					215					220				
Arg	Ala	Ile	Arg	Gln	Ala	Arg	Ala	Arg	Ala	Arg	Leu	Pro	Val	Thr	Thr
225					230				235						240
Trp	Arg	Ile	Ser	Ala	Gly	Ser	Gly	Gly	Gln	Ala	Glu	Arg	Thr	Ile	Ala
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	275						280					285			
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&lt;210&gt; 15

&lt;211&gt; 1316

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 15

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&lt;210&gt; 16

&lt;211&gt; 265

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 16

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Gln	Ile	Ser	Leu	Leu	Arg	Ala	Phe	Phe	Tyr	Val	Ala	Ala	Gln	Leu	Val
			85					90					95		
Gly	Ala	Ile	Ala	Gly	Ala	Gly	Ile	Leu	Tyr	Gly	Val	Ala	Pro	Leu	Asn
		100					105					110			
Ala	Arg	Gly	Asn	Leu	Ala	Val	Asn	Ala	Leu	Asn	Asn	Asn	Thr	Thr	Gln
	115						120					125			
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Pro	Ala	Leu	Ser	Ile	Gly	Leu	Ser	Val	Thr	Leu	Gly	His	Leu	Val	Gly
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Gly	Thr	Tyr	Glu	Pro	Asp	Glu	Asp	Trp	Glu	Glu	Gln	Arg	Glu	Glu	Arg
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Lys	Lys	Thr	Met	Glu	Leu	Thr	Thr	Arg							
		260						265							

&lt;210&gt; 17

&lt;211&gt; 1258

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 17

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 <212> PRT  
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 <212> PRT  
 <213> Homo sapiens

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 35 40 45  
 Asn Ser Glu Ala Cys Arg Asp Gly Leu Arg Ala Val Met Glu Cys Arg  
 50 55 60  
 Asn Val Thr His Leu Leu Gln Gln Glu Leu Thr Glu Ala Gln Lys Gly  
 65 70 75 80  
 Phe Gln Asp Val Glu Ala Gln Ala Ala Thr Cys Asn His Thr Val Met  
 85 90 95  
 Ala Leu Met Ala Ser Leu Asp Ala Glu Lys Ala Gln Gly Gln Lys Lys  
 100 105 110  
 Val Glu Glu Leu Glu Gly Glu Ile Thr Thr Leu Asn His Lys Leu Gln  
 115 120 125

Asp Ala Ser Ala Glu Val Glu Arg Leu Arg Arg Glu Asn Gln Val Leu  
 130 135 140  
 Ser Val Arg Ile Ala Asp Lys Lys Tyr Tyr Pro Ser Ser Gln Asp Ser  
 145 150 155 160  
 Ser Ser Ala Ala Ala Pro Gln Leu Leu Ile Val Leu Leu Gly Leu Ser  
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 Ala Leu Leu Gln  
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&lt;210&gt; 21

&lt;211&gt; 4859

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 21

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&lt;210&gt; 22

&lt;211&gt; 244

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 22

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50          55          60
Lys Ser Leu Leu Asp Leu Asn Lys Tyr Arg Pro Ile Gln Thr Pro Ser
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Leu	Pro	Lys	Pro	Pro	Lys	Pro	Val	Ser	Lys	Met	Arg	Met	Ala	Thr	Pro
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Ser	Phe	Pro	Glu	Asn	Leu	Arg	His	Leu	Lys	Asn	Thr	Met	Glu	Thr	Ile
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&lt;211&gt; 1615

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 25

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<213> Homo sapiens
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&lt;210&gt; 27

&lt;211&gt; 2103

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 27

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&lt;210&gt; 30

&lt;211&gt; 184

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 30

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Thr Leu Leu Pro Ala Ala Glu Gly Lys Lys Lys Gly Ser Gln Gly Ala
20          25          30
Ile Pro Pro Pro Asp Lys Ala Gln His Asn Asp Ser Glu Gln Thr Gln
35          40          45
Ser Pro Gln Gln Pro Gly Ser Arg Asn Arg Gly Arg Gly Gln Gly Arg

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Gln Pro Leu Lys	Gln Thr Ile His Glu Glu Gly	Cys Asn Ser Arg Thr		
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Ile Ile Asn Arg	Phe Cys Tyr Gly Gln Cys Asn	Ser Phe Tyr Ile Pro		
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Arg His Ile Arg	Lys Glu Glu Gly Ser Phe Gln	Ser Cys Ser Phe Cys		
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&lt;210&gt; 31

&lt;211&gt; 3443

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 31

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&lt;210&gt; 32

&lt;211&gt; 211

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 32

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Gly Leu Trp Met Ser Cys Val Ser Gln Ser Thr Gly Gln Ile Gln Cys
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Lys Val Phe Asp Ser Leu Asn Leu Ser Ser Thr Leu Gln Ala Thr
          65          70          75          80
Arg Ala Leu Met Val Val Gly Ile Leu Leu Gly Val Ile Ala Ile Phe
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Val Ala Thr Val Gly Met Lys Cys Met Lys Cys Leu Glu Asp Asp Glu
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Val Gln Lys Met Arg Met Ala Val Ile Gly Gly Ala Ile Phe Leu Leu
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          165          170          175
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<211> 4318  
<212> DNA  
<213> Homo sapiens

<400> 33

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&lt;210&gt; 34

&lt;211&gt; 253

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 34

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Ile	Lys	Gly	Lys	Pro	Gly	Pro	Gln	Gly	Tyr	Pro	Gly	Val	Gly	Lys	Pro
145					150					155					160
Gly	Met	Pro	Gly	Met	Pro	Gly	Lys	Pro	Gly	Ala	Met	Gly	Met	Pro	Gly
				165					170					175	
Ala	Lys	Gly	Glu	Ile	Gly	Gln	Lys	Gly	Glu	Ile	Gly	Pro	Met	Gly	Ile
			180					185					190		
Pro	Gly	Pro	Gln	Gly	Pro	Pro	Gly	Pro	His	Gly	Leu	Pro	Gly	Ile	Gly
			195				200					205			
Lys	Pro	Gly	Gly	Pro	Gly	Leu	Pro	Gly	Gln	Pro	Gly	Pro	Lys	Gly	Asp
	210					215					220				
Arg	Gly	Pro	Lys	Gly	Leu	Pro	Gly	Pro	Gln	Gly	Leu	Arg	Gly	Pro	Lys
225					230					235					240
Gly	Asp	Lys	Gly	Phe	Gly	Met	Pro	Gly	Ala	Pro	Gly	Val	Lys	Gly	Pro
				245					250					255	
Pro	Gly	Met	His	Gly	Leu	Pro	Gly	Pro	Val	Gly	Leu	Pro	Gly	Val	Gly
			260					265						270	
Lys	Pro	Gly	Val	Thr	Gly	Phe	Pro	Gly	Pro	Gln	Gly	Pro	Leu	Gly	Lys
			275				280					285			
Pro	Gly	Ala	Pro	Gly	Glu	Pro	Gly	Arg	Gln	Gly	Pro	Ile	Gly	Val	Pro
	290					295					300				
Gly	Val	Gln	Gly	Pro	Pro	Gly	Ile	Pro	Gly	Ile	Gly	Lys	Pro	Gly	Gln
305					310					315					320
Asp	Gly	Ile	Pro	Gly	Gln	Pro	Gly	Phe	Pro	Gly	Gly	Lys	Gly	Glu	Gln
				325					330					335	
Gly	Leu	Pro	Gly	Leu	Pro	Gly	Ala	Pro	Gly	Leu	Pro	Gly	Ile	Gly	Lys
			340					345					350		
Pro	Gly	Phe	Pro	Gly	Pro	Lys	Gly	Asp	Arg	Gly	Met	Gly	Gly	Val	Pro
			355				360					365			
Gly	Ala	Leu	Gly	Pro	Arg	Gly	Glu	Lys	Gly	Pro	Ile	Gly	Ser	Pro	Gly
	370					375					380				
Ile	Gly	Gly	Ser	Pro	Gly	Glu	Pro	Gly	Leu	Pro	Gly	Ile	Pro	Gly	Pro
385					390					395					400
Met	Gly	Pro	Pro	Gly	Ala	Ile	Gly	Phe	Pro	Gly	Pro	Lys	Gly	Glu	Gly
				405					410					415	
Gly	Ile	Val	Gly	Pro	Gln	Gly	Pro	Pro	Gly	Pro	Lys	Gly	Glu	Pro	Gly
			420					425					430		
Leu	Gln	Gly	Phe	Pro	Gly	Lys	Pro	Gly	Phe	Leu	Gly	Glu	Val	Gly	Pro
			435				440					445			
Pro	Gly	Met	Arg	Gly	Phe	Pro	Gly	Pro	Ile	Gly	Pro	Lys	Gly	Glu	His
	450					455					460				
Gly	Gln	Lys	Gly	Val	Pro	Gly	Leu	Pro	Gly	Val	Pro	Gly	Leu	Leu	Gly
465					470					475					480
Pro	Lys	Gly	Glu	Pro	Gly	Ile	Pro	Gly	Asp	Gln	Gly	Leu	Gln	Gly	Pro
				485					490					495	
Pro	Gly	Ile	Pro	Gly	Ile	Gly	Gly	Pro	Ser	Gly	Pro	Ile	Gly	Pro	Pro
			500					505					510		
Gly	Ile	Pro	Gly	Pro	Lys	Gly	Glu	Pro	Gly	Leu	Pro	Gly	Pro	Pro	Gly

	515		520		525
Phe	Pro Gly Ile Gly Lys	Pro Gly Val Ala Gly	Leu His Gly	Pro	Pro
	530	535	540		
Gly	Lys Pro Gly Ala Leu	Gly Pro Gln Gly Gln	Pro Gly Leu	Pro	Gly
545	550	555			560
Pro	Pro Gly Pro Pro Gly	Pro Pro Gly Pro	Pro Ala Val	Met	Pro Pro
	565	570			575
Thr	Pro Pro Pro Gln Gly	Glu Tyr Leu Pro	Asp Met Gly	Leu	Gly Ile
	580	585			590
Asp	Gly Val Lys Pro Pro	His Ala Thr Gly	Ala Lys Lys	Gly Lys	Asn
	595	600			605
Gly	Gly Pro Ala Tyr Glu	Met Pro Ala Phe	Thr Ala Glu	Leu Thr	Ala
	610	615			620
Pro	Phe Pro Pro Val Gly	Gly Pro Val Lys	Phe Asn Lys	Leu Leu	Tyr
625	630	635			640
Asn	Gly Arg Gln Asn Tyr	Asn Pro Gln Thr	Gly Ile Phe	Thr Cys	Glu
	645	650			655
Val	Pro Gly Val Tyr Tyr	Phe Ala Tyr His	Val His Cys	Lys Gly	Gly
	660	665			670
Asn	Val Trp Val Ala Leu	Phe Lys Asn Asn	Glu Pro Val	Met Tyr	Thr
	675	680			685
Tyr	Asp Glu Tyr Lys Lys	Gly Phe Leu Asp	Gln Ala Ser	Gly Ser	Ala
	690	695			700
Val	Leu Leu Leu Arg Pro	Gly Asp Arg Val	Phe Leu Gln	Met Pro	Ser
705	710	715			720
Glu	Gln Ala Ala Gly Leu	Tyr Ala Gly Gln	Tyr Val His	Ser Ser	Phe
	725	730			735
Ser	Gly Tyr Leu Leu Tyr	Pro Met			
	740				

&lt;210&gt; 41

&lt;211&gt; 5064

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 41

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agaggatttta cagggtgggg ggacagaggg gcagcaggaa ccagaaggga gacagtggcg 120
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cgagaccaag agcgcgcggg tcaaagggtc cagctttcac cccaaaagac cttggatcct 540
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tcttttcaca ttgcttgggc acttagatta tattcgacc acgttttttc atcatgaata 780
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aactcttaat catctcccat ttctcttaga catttaaatt tcaaggcagg taccctctgt 4920
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&lt;210&gt; 42

&lt;211&gt; 1224

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 42

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Met Leu Thr Lys Phe Glu Thr Lys Ser Ala Arg Val Lys Gly Leu Ser
 1          5          10          15
Phe His Pro Lys Arg Pro Trp Ile Leu Thr Ser Leu His Asn Gly Val
 20          25          30
Ile Gln Leu Trp Asp Tyr Arg Met Cys Thr Leu Ile Asp Lys Phe Asp
 35          40          45
Glu His Asp Gly Pro Val Arg Gly Ile Asp Phe His Lys Gln Gln Pro
 50          55          60
Leu Phe Val Ser Gly Gly Asp Asp Tyr Lys Ile Lys Val Trp Asn Tyr
 65          70          75          80
Lys Leu Arg Arg Cys Leu Phe Thr Leu Leu Gly His Leu Asp Tyr Ile
 85          90          95
Arg Thr Thr Phe Phe His His Glu Tyr Pro Trp Ile Leu Ser Ala Ser
100          105          110
Asp Asp Gln Thr Ile Arg Val Trp Asn Trp Gln Ser Arg Thr Cys Val
115          120          125
Cys Val Leu Thr Gly His Asn His Tyr Val Met Cys Ala Gln Phe His
130          135          140
Pro Thr Glu Asp Leu Val Val Ser Ala Ser Leu Asp Gln Thr Val Arg
145          150          155          160
Val Trp Asp Ile Ser Gly Leu Arg Lys Lys Asn Leu Ser Pro Gly Ala
165          170          175
Val Glu Ser Asp Val Arg Gly Ile Thr Gly Val Asp Leu Phe Gly Thr
180          185          190
Thr Asp Ala Val Val Lys His Val Leu Glu Gly His Asp Arg Gly Val
195          200          205
Asn Trp Ala Ala Phe His Pro Thr Met Pro Leu Ile Val Ser Gly Ala
210          215          220
Asp Asp Arg Gln Val Lys Ile Trp Arg Met Asn Glu Ser Lys Ala Trp
225          230          235          240
Glu Val Asp Thr Cys Arg Gly His Tyr Asn Asn Val Ser Cys Ala Val
245          250          255
Phe His Pro Arg Gln Glu Leu Ile Leu Ser Asn Ser Glu Asp Lys Ser
260          265          270
Ile Arg Val Trp Asp Met Ser Lys Arg Thr Gly Val Gln Thr Phe Arg
275          280          285
Arg Asp His Asp Arg Phe Trp Val Leu Ala Ala His Pro Asn Leu Asn
290          295          300
Leu Phe Ala Ala Gly His Asp Gly Gly Met Ile Val Phe Lys Leu Glu
305          310          315          320
Arg Glu Arg Pro Ala Tyr Ala Val His Gly Asn Met Leu His Tyr Val
325          330          335
Lys Asp Arg Phe Leu Arg Gln Leu Asp Phe Asn Ser Ser Lys Asp Val
340          345          350
Ala Val Met Gln Leu Arg Ser Gly Ser Lys Phe Pro Val Phe Asn Met
355          360          365
Ser Tyr Asn Pro Ala Glu Asn Ala Val Leu Leu Cys Thr Arg Ala Ser
370          375          380

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Asn	Leu	Glu	Asn	Ser	Thr	Tyr	Asp	Leu	Tyr	Thr	Ile	Pro	Lys	Asp	Ala
385					390					395					400
Asp	Ser	Gln	Asn	Pro	Asp	Ala	Pro	Glu	Gly	Lys	Arg	Ser	Ser	Gly	Leu
			405					410						415	
Thr	Ala	Val	Trp	Val	Ala	Arg	Asn	Arg	Phe	Ala	Val	Leu	Asp	Arg	Met
		420					425						430		
His	Ser	Leu	Leu	Ile	Lys	Asn	Leu	Lys	Asn	Glu	Ile	Thr	Lys	Lys	Val
	435					440					445				
Gln	Val	Pro	Asn	Cys	Asp	Glu	Ile	Phe	Tyr	Ala	Gly	Thr	Gly	Asn	Leu
	450				455						460				
Leu	Leu	Arg	Asp	Ala	Asp	Ser	Ile	Thr	Leu	Phe	Asp	Val	Gln	Gln	Lys
465					470					475					480
Arg	Thr	Leu	Ala	Ser	Val	Lys	Ile	Ser	Lys	Val	Lys	Tyr	Val	Ile	Trp
			485						490					495	
Ser	Ala	Asp	Met	Ser	His	Val	Ala	Leu	Leu	Ala	Lys	His	Ala	Ile	Val
		500						505					510		
Ile	Cys	Asn	Arg	Lys	Leu	Asp	Ala	Leu	Cys	Asn	Ile	His	Glu	Asn	Ile
	515					520						525			
Arg	Val	Lys	Ser	Gly	Ala	Trp	Asp	Glu	Ser	Gly	Val	Phe	Ile	Tyr	Thr
	530				535						540				
Thr	Ser	Asn	His	Ile	Lys	Tyr	Ala	Val	Thr	Thr	Gly	Asp	His	Gly	Ile
545					550					555					560
Ile	Arg	Thr	Leu	Asp	Leu	Pro	Ile	Tyr	Val	Thr	Arg	Val	Lys	Gly	Asn
			565						570					575	
Asn	Val	Tyr	Cys	Leu	Asp	Arg	Glu	Cys	Arg	Pro	Arg	Val	Leu	Thr	Ile
		580						585					590		
Asp	Pro	Thr	Glu	Phe	Lys	Phe	Lys	Leu	Ala	Leu	Ile	Asn	Arg	Lys	Tyr
	595						600					605			
Asp	Glu	Val	Leu	His	Met	Val	Arg	Asn	Ala	Lys	Leu	Val	Gly	Gln	Ser
	610					615					620				
Ile	Ile	Ala	Tyr	Leu	Gln	Lys	Lys	Gly	Tyr	Pro	Glu	Val	Ala	Leu	His
625					630					635					640
Phe	Val	Lys	Asp	Glu	Lys	Thr	Arg	Phe	Ser	Leu	Ala	Leu	Glu	Cys	Gly
			645						650					655	
Asn	Ile	Glu	Ile	Ala	Leu	Glu	Ala	Ala	Lys	Ala	Leu	Asp	Asp	Lys	Asn
			660					665					670		
Cys	Trp	Glu	Lys	Leu	Gly	Glu	Val	Ala	Leu	Leu	Gln	Gly	Asn	His	Gln
	675						680					685			
Ile	Val	Glu	Met	Cys	Tyr	Gln	Arg	Thr	Lys	Asn	Phe	Asp	Lys	Val	Ser
	690					695					700				
Phe	Leu	Tyr	Leu	Ile	Thr	Gly	Asn	Leu	Glu	Lys	Leu	Arg	Lys	Met	Met
705					710					715					720
Lys	Ile	Ala	Glu	Ile	Arg	Lys	Asp	Met	Ser	Gly	His	Tyr	Gln	Asn	Ala
			725						730					735	
Leu	Tyr	Leu	Gly	Asp	Val	Ser	Glu	Arg	Val	Arg	Ile	Leu	Lys	Asn	Cys
			740					745					750		
Gly	Gln	Lys	Ser	Leu	Ala	Tyr	Leu	Thr	Ala	Ala	Thr	His	Gly	Leu	Asp
	755						760					765			
Glu	Glu	Ala	Glu	Ser	Leu	Lys	Glu	Thr	Phe	Asp	Pro	Glu	Lys	Glu	Thr
	770					775					780				
Ile	Pro	Asp	Ile	Asp	Pro	Asn	Ala	Lys	Leu	Leu	Gln	Pro	Pro	Ala	Pro
785					790					795					800
Ile	Met	Pro	Leu	Asp	Thr	Asn	Trp	Pro	Leu	Leu	Thr	Val	Ser	Lys	Gly
			805						810					815	
Phe	Phe	Glu	Gly	Thr	Ile	Ala	Ser	Lys	Gly	Lys	Gly	Gly	Ala	Leu	Ala
			820					825					830		
Ala	Asp	Ile	Asp	Ile	Asp	Thr	Val	Gly	Thr	Glu	Gly	Trp	Gly	Glu	Asp
	835					840						845			
Ala	Glu	Leu	Gln	Leu	Asp	Glu	Asp	Gly	Phe	Val	Glu	Ala	Thr	Glu	Gly

850	855	860
Leu Gly Asp Asp Ala	Leu Gly Lys Gly Gln Glu	Glu Gly Gly Gly Trp
865	870	875
Asp Val Glu Glu Asp	Leu Glu Leu Pro Pro	Glu Leu Asp Ile Ser Pro
885	890	895
Gly Ala Ala Gly Gly	Ala Glu Asp Gly Phe Phe	Val Pro Pro Thr Lys
900	905	910
Gly Thr Ser Pro Thr	Gln Ile Trp Cys Asn Asn	Ser Gln Leu Pro Val
915	920	925
Asp His Ile Leu Ala	Gly Ser Phe Glu Thr Ala	Met Arg Leu Leu His
930	935	940
Asp Gln Val Gly Val	Ile Gln Phe Gly Pro Tyr	Lys Gln Leu Phe Leu
945	950	955
Gln Thr Tyr Ala Arg	Gly Arg Thr Thr Tyr	Gln Ala Leu Pro Cys Leu
965	970	975
Pro Ser Met Tyr Gly	Tyr Pro Asn Arg Asn	Trp Lys Asp Ala Gly Leu
980	985	990
Lys Asn Gly Val Pro	Ala Val Gly Leu Lys	Leu Asn Asp Leu Ile Gln
995	1000	1005
Arg Leu Gln Leu Cys	Tyr Gln Leu Thr Thr	Val Gly Lys Phe Glu Glu
1010	1015	1020
Ala Val Glu Lys Phe	Arg Ser Ile Leu Leu	Ser Val Pro Leu Leu Val
1025	1030	1035
Val Asp Asn Lys Gln	Glu Ile Ala Glu Ala	Gln Gln Leu Ile Thr Ile
1045	1050	1055
Cys Arg Glu Tyr Ile	Val Gly Leu Ser Val	Glu Thr Glu Arg Lys Lys
1060	1065	1070
Leu Pro Lys Glu Thr	Leu Glu Gln Gln Lys	Arg Ile Cys Glu Met Ala
1075	1080	1085
Ala Tyr Phe Thr His	Ser Asn Leu Gln Pro	Val His Met Ile Leu Val
1090	1095	1100
Leu Arg Thr Ala Leu	Asn Leu Phe Phe Lys	Leu Lys Asn Phe Lys Thr
1105	1110	1115
Ala Ala Thr Phe Ala	Arg Arg Leu Leu Glu	Leu Gly Pro Lys Pro Glu
1125	1130	1135
Val Ala Gln Gln Thr	Arg Lys Ile Leu Ser	Ala Cys Glu Lys Asn Pro
1140	1145	1150
Thr Asp Ala Tyr Gln	Leu Asn Tyr Asp Met	His Asn Pro Phe Asp Ile
1155	1160	1165
Cys Ala Ala Ser Tyr	Arg Pro Ile Tyr Arg	Gly Lys Pro Val Glu Lys
1170	1175	1180
Cys Pro Leu Ser Gly	Ala Cys Tyr Ser Pro	Glu Phe Lys Gly Gln Ile
1185	1190	1195
Cys Arg Val Thr Thr	Val Thr Glu Ile Gly	Lys Asp Val Ile Gly Leu
1205	1210	1215
Arg Ile Ser Pro Leu	Gln Phe Arg	
1220		

&lt;210&gt; 43

&lt;211&gt; 266

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 43

```

atgcccaagt gtcccaagtg caacaaggag gtgtacttcg ccgagagggt gacctctctg 60
ggcaaggact ggcatcggcc ctgcctgaag tgcgagaaat gtgggaagac gctgacctct 120
gggggccacg ctgagcacga aggcaaacc tactgcaacc acccctgcta cgcagccatg 180
tttgggccta aaggcttttg gcggggcgga gccgagagcc acactttcaa gtaaaccagg 240

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266

<210> 44  
 <211> 77  
 <212> PRT  
 <213> Homo sapiens

<400> 44  
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 1 5 10 15  
 Val Thr Ser Leu Gly Lys Asp Trp His Arg Pro Cys Leu Lys Cys Glu  
 20 25 30  
 Lys Cys Gly Lys Thr Leu Thr Ser Gly Gly His Ala Glu His Glu Gly  
 35 40 45  
 Lys Pro Tyr Cys Asn His Pro Cys Tyr Ala Ala Met Phe Gly Pro Lys  
 50 55 60  
 Gly Phe Gly Arg Gly Gly Ala Glu Ser His Thr Phe Lys  
 65 70 75

<210> 45  
 <211> 2312  
 <212> DNA  
 <213> Homo sapiens

<400> 45  
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 ctctcgtggtc ctctcgtccc tctgcagccg gccggccgctc ggccagaact gcagcgggcc 240  
 gtgccggtgc ccggacgagc cggcgcccgcg ctgcccggcg ggcgtgagcc tcgtgctgga 300  
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 cccctgcgac ccgcacaagg gcctcttctg tgacttcggc tccccggcca accgcaagat 420  
 cggcgtgtgc accgccaaag atggtgctcc ctgcatcttc ggtggtagcg tgtaccgcag 480  
 cggagagtcc ttccagagca gctgcaagta ccagtgcacg tgccctggacg gggcggtggg 540  
 ctgcatgccc ctgtgcagca tggacgttcg tctgcccagc cctgactgcc ccttcccag 600  
 gaggtcaag ctgcccgga aatgctgcga ggagtgggtg tgtgacgagc ccaaggacca 660  
 aaccgtggtt gggcctgccc tcgcggctta ccgactggaa gacacgtttg gcccagaccc 720  
 aactatgatt agagccaact gcctggtcca gaccacagag tggagcgcct gttccaagac 780  
 ctgtgggatg ggcattctcca cccgggttac caatgacaac gcctcctgca ggctagagaa 840  
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 gggcaaaaag tgcattccgt ctcccaaaat ctccaagcct atcaagtttg agctttcttg 960  
 ctgcaccagc atgaagacat accgagctaa attctgtgga gtatgtaccg acggccgatg 1020  
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 ttgtgccttt ttatttttgt ttttaatgct ttgatatttc aatgttagcc tcaatttctg 1920  
 aacaccatag gtagaatgta aagcttgtct gatcgttcaa agcatgaaat ggatacttat 1980

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acctggaagc atttgtttct actttgatat gactgttttt cggacagttt atttgttgag 2220
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aaaaaaaaa aaaaacgaca gcaacggaat tc 2312

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&lt;210&gt; 46

&lt;211&gt; 349

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 46

```

Met Thr Ala Ala Ser Met Gly Pro Val Arg Val Ala Phe Val Val Leu
 1          5          10          15
Leu Ala Leu Cys Ser Arg Pro Ala Val Gly Gln Asn Cys Ser Gly Pro
 20          25          30
Cys Arg Cys Pro Asp Glu Pro Ala Pro Arg Cys Pro Ala Gly Val Ser
 35          40          45
Leu Val Leu Asp Gly Cys Gly Cys Cys Arg Val Cys Ala Lys Gln Leu
 50          55          60
Gly Glu Leu Cys Thr Glu Arg Asp Pro Cys Asp Pro His Lys Gly Leu
 65          70          75          80
Phe Cys Asp Phe Gly Ser Pro Ala Asn Arg Lys Ile Gly Val Cys Thr
 85          90          95
Ala Lys Asp Gly Ala Pro Cys Ile Phe Gly Gly Thr Val Tyr Arg Ser
100          105          110
Gly Glu Ser Phe Gln Ser Ser Cys Lys Tyr Gln Cys Thr Cys Leu Asp
115          120          125
Gly Ala Val Gly Cys Met Pro Leu Cys Ser Met Asp Val Arg Leu Pro
130          135          140
Ser Pro Asp Cys Pro Phe Pro Arg Arg Val Lys Leu Pro Gly Lys Cys
145          150          155          160
Cys Glu Glu Trp Val Cys Asp Glu Pro Lys Asp Gln Thr Val Val Gly
165          170          175
Pro Ala Leu Ala Tyr Arg Leu Glu Asp Thr Phe Gly Pro Asp Pro
180          185          190
Thr Met Ile Arg Ala Asn Cys Leu Val Gln Thr Thr Glu Trp Ser Ala
195          200          205
Cys Ser Lys Thr Cys Gly Met Gly Ile Ser Thr Arg Val Thr Asn Asp
210          215          220
Asn Ala Ser Cys Arg Leu Glu Lys Gln Ser Arg Leu Cys Met Val Arg
225          230          235          240
Pro Cys Glu Ala Asp Leu Glu Glu Asn Ile Lys Lys Gly Lys Lys Cys
245          250          255
Ile Arg Thr Pro Lys Ile Ser Lys Pro Ile Lys Phe Glu Leu Ser Gly
260          265          270
Cys Thr Ser Met Lys Thr Tyr Arg Ala Lys Phe Cys Gly Val Cys Thr
275          280          285
Asp Gly Arg Cys Cys Thr Pro His Arg Thr Thr Thr Leu Pro Val Glu
290          295          300
Phe Lys Cys Pro Asp Gly Glu Val Met Lys Lys Asn Met Met Phe Ile
305          310          315          320
Lys Thr Cys Ala Cys His Tyr Asn Cys Pro Gly Asp Asn Asp Ile Phe
325          330          335
Glu Ser Leu Tyr Tyr Arg Lys Met Tyr Gly Asp Met Ala
340          345

```

<210> 47  
 <211> 3025  
 <212> DNA  
 <213> Homo sapiens

<400> 47

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agtcttttgc tttgatgggtg gtggatgaac agcaaaggct gacggcacag ctcacccttc 180
aaagacagaa aatccaagag ctgaccacaa atgcaaagga aacacatacc aaactagccc 240
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aaacgcagac cacaaagttt caccaagacc aagacacaat tatggcgaag ctaccaaatg 360
aggacagtca aaatcgccag cttcaacaaa agctggcagc actcagccgg cagattgatg 420
agttagaaga gacaaacagg tcttttacgaa aagcagaaga ggagctgcaa gatataaaa 480
aaaaaatcag taagggagaa tatggaaacg ctggtatcat ggctgaagtg gaagagctca 540
taaaaatgga ggagcagtg cagagatctca ataagaggct tgaaaggag acgttacaga 600
gtaaagactt taaactagag gttgaaaaag tcagtaaaag aattatggct ctggaaaagg 660
tagaagacgc tttcaacaaa agcaaacaa aatgtactc tctgaaatgc aatttagaaa 720
aagaaaggat gaccacaaag cagttgtctc aagaactgga gagtttaaaa gtaaggatca 780
aagagctaga agccattgaa agtcggctag aaaagacaga attcactcta aaagaggatt 840
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aattaaagaa aactgaagat aaattacaag ctgcttcttc tcagcttcaa gtggagcaaa 960
ataaagtaac aacagttact gagaagttaa ttgaggaaac taaaagggcg ctcaagtcca 1020
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<210> 48

&lt;211&gt; 752

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 48

```

Met Val Val Asp Glu Gln Gln Arg Leu Thr Ala Gln Leu Thr Leu Gln
 1          5          10          15
Arg Gln Lys Ile Gln Glu Leu Thr Thr Asn Ala Lys Glu Thr His Thr
 20          25          30
Lys Leu Ala Leu Ala Glu Ala Arg Val Gln Glu Glu Glu Gln Lys Ala
 35          40          45
Thr Arg Leu Glu Lys Glu Leu Gln Thr Gln Thr Thr Lys Phe His Gln
 50          55          60
Asp Gln Asp Thr Ile Met Ala Lys Leu Thr Asn Glu Asp Ser Gln Asn
 65          70          75          80
Arg Gln Leu Gln Gln Lys Leu Ala Ala Leu Ser Arg Gln Ile Asp Glu
 85          90          95
Leu Glu Glu Thr Asn Arg Ser Leu Arg Lys Ala Glu Glu Glu Leu Gln
100          105          110
Asp Ile Lys Glu Lys Ile Ser Lys Gly Glu Tyr Gly Asn Ala Gly Ile
115          120          125
Met Ala Glu Val Glu Glu Leu Ile Lys Met Glu Glu Gln Cys Arg Asp
130          135          140
Leu Asn Lys Arg Leu Glu Arg Glu Thr Leu Gln Ser Lys Asp Phe Lys
145          150          155          160
Leu Glu Val Glu Lys Leu Ser Lys Arg Ile Met Ala Leu Glu Lys Leu
165          170          175
Glu Asp Ala Phe Asn Lys Ser Lys Gln Glu Cys Tyr Ser Leu Lys Cys
180          185          190
Asn Leu Glu Lys Glu Arg Met Thr Thr Lys Gln Leu Ser Gln Glu Leu
195          200          205
Glu Ser Leu Lys Val Arg Ile Lys Glu Leu Glu Ala Ile Glu Ser Arg
210          215          220
Leu Glu Lys Thr Glu Phe Thr Leu Lys Glu Asp Leu Thr Lys Leu Lys
225          230          235          240
Thr Leu Thr Val Met Phe Val Asp Glu Arg Lys Thr Met Ser Glu Lys
245          250          255
Leu Lys Lys Thr Glu Asp Lys Leu Gln Ala Ala Ser Ser Gln Leu Gln
260          265          270
Val Glu Gln Asn Lys Val Thr Thr Val Thr Glu Lys Leu Ile Glu Glu
275          280          285
Thr Lys Arg Ala Leu Lys Ser Lys Thr Asp Val Glu Glu Lys Met Tyr
290          295          300
Ser Val Thr Lys Glu Arg Asp Asp Leu Lys Asn Lys Leu Lys Ala Glu
305          310          315          320
Glu Glu Lys Gly Asn Asp Leu Leu Ser Arg Val Asn Met Leu Lys Asn
325          330          335
Arg Leu Gln Ser Leu Glu Ala Ile Glu Lys Asp Phe Leu Lys Asn Lys
340          345          350
Leu Asn Gln Asp Ser Gly Lys Ser Thr Thr Ala Leu His Gln Glu Asn
355          360          365
Asn Lys Ile Lys Glu Leu Ser Gln Glu Val Glu Arg Leu Lys Leu Lys
370          375          380
Leu Lys Asp Met Lys Ala Ile Glu Asp Asp Leu Met Lys Thr Glu Asp
385          390          395          400
Glu Tyr Glu Thr Leu Glu Arg Arg Tyr Ala Asn Glu Arg Asp Lys Ala
405          410          415
Gln Phe Leu Ser Lys Glu Leu Glu His Val Lys Met Glu Leu Ala Lys
420          425          430

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Tyr	Lys	Leu	Ala	Glu	Lys	Thr	Glu	Thr	Ser	His	Glu	Gln	Trp	Leu	Phe
		435					440					445			
Lys	Arg	Leu	Gln	Glu	Glu	Glu	Ala	Lys	Ser	Gly	His	Leu	Ser	Arg	Glu
		450				455					460				
Val	Asp	Ala	Leu	Lys	Glu	Lys	Ile	His	Glu	Tyr	Met	Ala	Thr	Glu	Asp
		465			470					475					480
Leu	Ile	Cys	His	Leu	Gln	Gly	Asp	His	Ser	Val	Cys	Lys	Lys	Lys	Leu
				485					490					495	
Asn	Gln	Gln	Glu	Asn	Arg	Asn	Arg	Asp	Leu	Gly	Arg	Glu	Ile	Glu	Asn
			500					505					510		
Leu	Thr	Lys	Glu	Leu	Glu	Arg	Tyr	Arg	His	Phe	Ser	Lys	Ser	Leu	Arg
		515					520					525			
Pro	Ser	Leu	Asn	Gly	Arg	Arg	Ile	Ser	Asp	Pro	Gln	Val	Phe	Ser	Lys
		530				535					540				
Glu	Val	Gln	Thr	Glu	Ala	Val	Asp	Asn	Glu	Pro	Pro	Asp	Tyr	Lys	Ser
				550						555					560
Leu	Ile	Pro	Leu	Glu	Arg	Ala	Val	Ile	Asn	Gly	Gln	Leu	Tyr	Glu	Glu
				565					570					575	
Ser	Glu	Asn	Gln	Asp	Glu	Asp	Pro	Asn	Asp	Glu	Gly	Ser	Val	Leu	Ser
			580						585				590		
Phe	Lys	Cys	Ser	Gln	Ser	Thr	Pro	Cys	Pro	Val	Asn	Arg	Lys	Leu	Trp
		595					600					605			
Ile	Pro	Trp	Met	Lys	Ser	Lys	Glu	Gly	His	Leu	Gln	Asn	Gly	Lys	Met
		610				615						620			
Gln	Thr	Lys	Pro	Asn	Ala	Asn	Phe	Val	Gln	Pro	Gly	Asp	Leu	Val	Leu
				630						635					640
Ser	His	Thr	Pro	Gly	Gln	Pro	Leu	His	Ile	Lys	Val	Thr	Pro	Asp	His
				645					650					655	
Val	Gln	Asn	Thr	Ala	Thr	Leu	Glu	Ile	Thr	Ser	Pro	Thr	Thr	Glu	Ser
			660					665					670		
Pro	His	Ser	Tyr	Thr	Ser	Thr	Ala	Val	Ile	Pro	Asn	Cys	Gly	Thr	Pro
		675					680					685			
Lys	Gln	Arg	Ile	Thr	Ile	Leu	Gln	Asn	Ala	Ser	Ile	Thr	Pro	Val	Lys
		690				695					700				
Ser	Lys	Thr	Ser	Thr	Glu	Asp	Leu	Met	Asn	Leu	Glu	Gln	Gly	Met	Ser
					710					715					720
Pro	Ile	Thr	Met	Ala	Thr	Phe	Ala	Arg	Ala	Gln	Thr	Pro	Glu	Ser	Cys
				725					730					735	
Gly	Ser	Leu	Thr	Pro	Glu	Arg	Thr	Met	Ser	Leu	Phe	Arg	Phe	Trp	Leu
			740					745					750		

&lt;210&gt; 49

&lt;211&gt; 1480

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 49

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cgctgctgat cgccacaccg tcttctggaa cagttcaaat cccaagttcc ggaatgagga 180
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tgaagaccgc tgcttgaggt tgaaggtgac tgctcagtggc aaaatcactc acagtcctca 540
ggcccatgtc aatccacagg agaagagact tgcagcagat gaccagagg tgccgggttct 600
acatagcatc ggtcacagtg ctgccccacg cctcttccca cttgcctgga ctgtgctgct 660

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ccagccctgg gaaccactcc caccacaggc ataagctatc acctagcagc ctcaaaacgg 840
gtcagtatta aggttttcaa ccggaaggag gccaaccagc ccgacagtgc catccccacc 900
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aagccaaaga aacaagctgt gcaggcatgg tcccttaagg cacagtggga gctgagctgg 1020
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&lt;210&gt; 50

&lt;211&gt; 205

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 50

```

Met Glu Phe Leu Trp Ala Pro Leu Leu Gly Leu Cys Cys Ser Leu Ala
1      5      10      15
Ala Ala Asp Arg His Thr Val Phe Trp Asn Ser Ser Asn Pro Lys Phe
20     25     30
Arg Asn Glu Asp Tyr Thr Ile His Val Gln Leu Asn Asp Tyr Val Asp
35     40     45
Ile Ile Cys Pro His Tyr Glu Asp His Ser Val Ala Asp Ala Ala Met
50     55     60
Glu Gln Tyr Ile Leu Tyr Leu Val Glu His Glu Tyr Gln Leu Cys
65     70     75     80
Gln Pro Gln Ser Lys Asp Gln Val Arg Trp Gln Cys Asn Arg Pro Ser
85     90     95
Ala Lys His Gly Pro Glu Lys Leu Ser Glu Lys Phe Gln Arg Phe Thr
100    105    110
Pro Phe Thr Leu Gly Lys Glu Phe Lys Glu Gly His Ser Tyr Tyr Tyr
115    120    125
Ile Ser Lys Pro Ile His Gln His Glu Asp Arg Cys Leu Arg Leu Lys
130    135    140
Val Thr Val Ser Gly Lys Ile Thr His Ser Pro Gln Ala His Val Asn
145    150    155    160
Pro Gln Glu Lys Arg Leu Ala Ala Asp Asp Pro Glu Val Arg Val Leu
165    170    175
His Ser Ile Gly His Ser Ala Ala Pro Arg Leu Phe Pro Leu Ala Trp
180    185    190
Thr Val Leu Leu Leu Pro Leu Leu Leu Leu Gln Thr Pro
195    200    205

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&lt;210&gt; 51

&lt;211&gt; 15952

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 51

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cacagagcag gccagtgtac ccagagccat ggcagccacg ctgggagccg gcacgcccc 120
caggccccag gccaggagca tagctggggg gtatgtggag gcctcggggc aggccccag 180
tgtctacgcc gccatggagc agggcctcct gcctgctggg ctctgggcagg ctctgctaga 240

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gcgtgccact	acgggctatc	ctgaccctta	cggcggtgag	aagctggccc	tctttcaggc	420
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&lt;210&gt; 52

&lt;211&gt; 5065

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 52

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Met Ala Ala Thr Leu Gly Ala Gly Thr Pro Pro Arg Pro Gln Ala Arg
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Ser Ile Ala Gly Val Tyr Val Glu Ala Ser Gly Gln Ala Gln Ser Val
20 25 30
Tyr Ala Ala Met Glu Gln Gly Leu Leu Pro Ala Gly Leu Gly Gln Ala
35 40 45
Leu Leu Glu Ala Gln Ala Ala Thr Gly Gly Leu Val Asp Leu Ala Arg
50 55 60
Gly Gln Leu Leu Pro Val Ser Lys Ala Leu Gln Gln Gly Leu Val Gly
65 70 75 80
Leu Glu Leu Lys Glu Lys Leu Leu Ala Ala Glu Arg Ala Thr Thr Gly
85 90 95
Tyr Pro Asp Pro Tyr Gly Gly Glu Lys Leu Ala Leu Phe Gln Ala Ile
100 105 110
Gly Lys Glu Val Val Asp Arg Ala Leu Gly Gln Ser Trp Leu Glu Val
115 120 125
Gln Leu Ala Thr Gly Gly Leu Val Asp Pro Ala Gln Gly Val Leu Val
130 135 140
Ala Pro Glu Pro Ala Cys His Gln Gly Leu Leu Asp Arg Glu Thr Trp
145 150 155 160
His Lys Leu Ser Glu Leu Glu Pro Gly Thr Gly Asp Leu Arg Phe Leu
165 170 175
Asn Pro Asn Thr Leu Glu Arg Leu Thr Tyr His Gln Leu Leu Glu Arg
180 185 190
Cys Val Arg Ala Pro Gly Ser Gly Leu Ala Leu Leu Pro Leu Lys Ile
195 200 205

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Thr	Phe	Arg	Ser	Met	Gly	Gly	Ala	Val	Ser	Ala	Ala	Glu	Leu	Leu	Glu
210					215					220					
Val	Gly	Ile	Leu	Asp	Glu	Gln	Ala	Val	Gln	Gly	Leu	Arg	Glu	Gly	Arg
225					230					235					240
Leu	Ala	Ala	Val	Asp	Val	Ser	Ala	Arg	Ala	Glu	Val	Arg	Arg	Tyr	Leu
				245					250					255	
Glu	Gly	Thr	Gly	Ser	Val	Ala	Gly	Val	Val	Leu	Leu	Pro	Glu	Gly	His
			260					265					270		
Lys	Lys	Ser	Phe	Phe	Gln	Ala	Ala	Thr	Glu	His	Leu	Leu	Pro	Met	Gly
		275						280					285		
Thr	Ala	Leu	Pro	Leu	Leu	Glu	Ala	Gln	Ala	Ala	Thr	His	Thr	Leu	Val
290						295					300				
Asp	Pro	Ile	Thr	Gly	Gln	Arg	Leu	Trp	Val	Asp	Glu	Ala	Val	Arg	Ala
305					310					315					320
Gly	Leu	Val	Ser	Pro	Glu	Leu	His	Glu	Gln	Leu	Leu	Val	Ala	Glu	Gln
				325					330					335	
Ala	Val	Thr	Gly	His	His	Asp	Pro	Phe	Ser	Gly	Ser	Gln	Ile	Pro	Leu
			340					345					350		
Phe	Gln	Ala	Met	Lys	Lys	Gly	Leu	Val	Asp	Arg	Pro	Leu	Ala	Leu	Arg
			355				360					365			
Leu	Leu	Asp	Ala	Gln	Leu	Ala	Thr	Gly	Gly	Leu	Val	Cys	Pro	Ala	Arg
370						375					380				
Arg	Leu	Arg	Leu	Pro	Leu	Glu	Ala	Ala	Leu	Arg	Cys	Gly	Cys	Leu	Asp
385					390					395					400
Glu	Asp	Thr	Gln	Arg	Gln	Leu	Ser	Gln	Ala	Gly	Ser	Phe	Ser	Asp	Gly
				405					410					415	
Thr	His	Gly	Gly	Leu	Arg	Tyr	Glu	Gln	Leu	Leu	Ala	Leu	Cys	Val	Thr
			420					425					430		
Asp	Pro	Glu	Thr	Gly	Leu	Ala	Phe	Leu	Pro	Leu	Ser	Gly	Gly	Pro	Arg
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Gly	Gly	Glu	Pro	Gln	Gly	Pro	Pro	Phe	Ile	Lys	Tyr	Ser	Thr	Arg	Gln
			450			455					460				
Ala	Leu	Ser	Thr	Ala	Thr	Ala	Thr	Val	Ser	Val	Gly	Lys	Phe	Arg	Gly
465					470					475					480
Arg	Pro	Val	Ser	Leu	Trp	Glu	Leu	Leu	Phe	Ser	Glu	Ala	Ile	Ser	Ser
				485					490					495	
Glu	Gln	Arg	Ala	Met	Leu	Ala	Gln	Gln	Tyr	Gln	Glu	Gly	Thr	Leu	Ser
			500					505					510		
Val	Glu	Lys	Leu	Ala	Ala	Glu	Leu	Ser	Ala	Thr	Leu	Glu	Gln	Ala	Ala
			515					520				525			
Ala	Thr	Ala	Arg	Val	Thr	Phe	Ser	Gly	Leu	Arg	Asp	Thr	Val	Thr	Pro
						535					540				
Gly	Glu	Leu	Leu	Lys	Ala	Glu	Ile	Ile	Asp	Gln	Asp	Leu	Tyr	Glu	Arg
545					550					555					560
Leu	Glu	His	Gly	Gln	Ala	Thr	Ala	Lys	Asp	Val	Gly	Ser	Leu	Ala	Ser
				565					570					575	
Ala	Gln	Arg	Tyr	Leu	Gln	Gly	Thr	Gly	Cys	Ile	Ala	Gly	Leu	Leu	Leu
			580					585					590		
Pro	Gly	Ser	Gln	Glu	Arg	Leu	Ser	Ile	Tyr	Glu	Ala	Arg	Cys	Lys	Gly
			595				600					605			
Leu	Leu	Arg	Pro	Gly	Thr	Ala	Leu	Ile	Leu	Leu	Glu	Ala	Gln	Ala	Ala
						615					620				
Thr	Gly	Phe	Ile	Ile	Asp	Pro	Lys	Ala	Asn	Lys	Gly	His	Ser	Val	Glu
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Glu	Ala	Leu	Arg	Ala	Ala	Val	Ile	Gly	Pro	Asp	Val	Phe	Ala	Lys	Leu
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Leu	Ser	Ala	Glu	Arg	Ala	Val	Thr	Gly	Tyr	Thr	Asp	Pro	Tyr	Thr	Gly
			660					665					670		
Gln	Gln	Ile	Ser	Leu	Phe	Gln	Ala	Met	Gln	Lys	Gly	Leu	Ile	Val	Arg

675	680	685
Glu His Gly Ile Arg Leu	Leu Glu Ala Gln Ile Ala	Thr Gly Gly Val
690	695	700
Ile Asp Pro Val His Ser	His Arg Val Pro Val Asp	Val Ala Tyr Arg
705	710	715
Arg Gly Tyr Phe Asp Gln	Met Leu Asn Leu Ile Leu	Leu Asp Pro Ser
725	730	735
Asp Asp Thr Lys Gly Phe	Phe Asp Pro Asn Thr His	Glu Asn Leu Thr
740	745	750
Tyr Leu Gln Leu Leu Glu	Arg Cys Val Arg Asp Pro	Glu Thr Gly Leu
755	760	765
Tyr Leu Leu Pro Leu Ser	Ser Thr Gln Ser Pro Leu	Val Asp Ser Ala
770	775	780
Thr Gln Gln Ala Phe Gln	Asn Leu Leu Leu Ser Val	Lys Tyr Gly Arg
785	790	795
Phe Gln Gly Gln Arg Val	Ser Ala Trp Glu Leu Ile	Asn Ser Glu Tyr
805	810	815
Phe Ser Glu Gly Arg Arg	Arg Gln Leu Leu Arg Arg	Tyr Arg Gln Arg
820	825	830
Glu Val Thr Leu Gly Gln	Val Ala Lys Leu Leu Glu	Ala Glu Thr Gln
835	840	845
Arg Gln Ala Asp Ile Met	Leu Pro Ala Leu Arg Ser	Arg Val Thr Val
850	855	860
His Gln Leu Leu Glu Ala	Gly Ile Ile Asp Gln Gln	Leu Leu Asp Gln
865	870	875
Val Leu Ala Gly Thr Ile	Ser Pro Glu Ala Leu Leu	Leu Met Asp Gly
885	890	895
Val Arg Arg Tyr Leu Cys	Gly Leu Gly Ala Val Gly	Gly Val Arg Leu
900	905	910
Leu Pro Ser Gly Gln Arg	Leu Ser Leu Tyr Gln Ala	Met Arg Gln Lys
915	920	925
Leu Leu Gly Pro Arg Val	Ala Leu Ala Leu Leu Glu	Ala Gln Ala Ala
930	935	940
Thr Gly Thr Ile Met Asp	Pro His Ser Pro Glu Ser	Leu Ser Val Asp
945	950	955
Glu Ala Val Arg Arg Gly	Val Val Gly Pro Glu Leu	Tyr Gly Arg Leu
965	970	975
Lys Arg Ala Glu Gly Ala	Ile Ala Gly Phe Arg Asp	Pro Phe Ser Gly
980	985	990
Lys Gln Val Ser Val Phe	Gln Ala Met Lys Lys Gly	Leu Ile Pro Trp
995	1000	1005
Glu Gln Ala Ala Arg Leu	Leu Glu Ala Gln Val Ala	Thr Gly Gly Ile
1010	1015	1020
Ile Asp Pro Thr Ser His	His His His Leu Pro Met	Pro Val Ala Ile Gln
1025	1030	1035
Arg Gly Tyr Val Asp Gln	Glu Met Glu Thr Ala Leu	Ser Ser Ser Ser
1045	1050	1055
Glu Thr Phe Pro Thr Pro	Asp Gly Gln Gly Arg Thr	Ser Tyr Ala Gln
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Leu Leu Glu Glu Cys Pro	Arg Asp Glu Thr Ser Gly	Leu His Leu Leu
1075	1080	1085
Pro Leu Pro Glu Ser Ala	Pro Ala Leu Pro Thr Glu	Glu Gln Val Gln
1090	1095	1100
Arg Ser Leu Gln Ala Val	Pro Gly Ala Lys Asp Gly	Thr Ser Leu Trp
1105	1110	1115
Asp Leu Leu Ser Ser Cys	His Phe Thr Glu Glu Gln	Arg Arg Gly Leu
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Leu Glu Asp Val Gln Glu	Gly Arg Thr Thr Val Pro	Gln Leu Leu Ala
1140	1145	1150

Ser Val Gln Arg Trp Val Gln Glu Thr Lys Leu Leu Ala Gln Ala Arg  
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 Thr Gln Ser Pro Ala Gln Val Ala Glu Gln Pro Ala Val Lys Ala Cys  
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 Val Gly Leu Val Gly Arg Glu Leu Ser Glu Gln Leu Gly Gln Ala Glu  
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 Asp Thr Gln Thr Ser Gln Val Leu Thr Ala Val Asp Lys Asp Asn Lys  
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 Phe Phe Phe Asp Pro Ser Ala Arg Asp Gln Val Thr Tyr Gln Gln Leu  
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 1395 1400 1405  
 Leu Pro Ser Asp Thr Val Leu Glu Val Asp Asp His Thr Ala Val Ala  
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 Leu Arg Ala Met Lys Val Pro Val Ser Thr Gly Arg Phe Lys Gly Cys  
 1425 1430 1435 1440  
 Ser Val Ser Leu Trp Asp Leu Leu Leu Ser Glu Tyr Val Gly Ala Asp  
 1445 1450 1455  
 Lys Arg Arg Glu Leu Val Ala Leu Cys Arg Ser Gly Arg Ala Ala Ala  
 1460 1465 1470  
 Leu Arg Gln Val Val Ser Ala Val Thr Ala Leu Val Glu Ala Ala Glu  
 1475 1480 1485  
 Arg Gln Pro Leu Gln Ala Thr Phe Arg Gly Leu Arg Lys Gln Val Ser  
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 Ala Arg Asp Leu Phe Arg Ala Gln Leu Ile Ser Arg Lys Thr Leu Asp  
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 Ser Val Lys Arg Ser Leu Glu Gly Gly Asn Phe Ile Ala Gly Val Leu  
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 Ile Gln Gly Thr Gln Glu Arg Met Ser Ile Pro Glu Ala Leu Arg Arg  
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 Leu Leu Ser Ala Glu Arg Ala Val Thr Gly Tyr Thr Asp Pro Tyr Thr

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Ile	Ile	Asp	Pro	Val	His	Ser	His	Arg	Val	Pro	Val	Asp	Val	Ala	Tyr		
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Arg	Cys	Gly	Tyr	Phe	Asp	Glu	Glu	Met	Asn	Arg	Ile	Leu	Ala	Asp	Pro		
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Ser	Asp	Asp	Thr	Lys	Gly	Phe	Phe	Asp	Pro	Asn	Thr	His	Glu	Asn	Leu		
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Gly	Ala	Gln	Ser	Gly	Gly	Leu	Glu	Lys	Leu	Leu	Glu	Ile	Ile	Thr	Thr		
	1795					1800					1805						
Thr	Ile	Glu	Glu	Thr	Glu	Thr	Gln	Asn	Gln	Gly	Ile	Lys	Val	Ala	Ala		
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Asp	Gln	Lys	Thr	Leu	His	Thr	Leu	Arg	Val	Gly	Arg	Thr	Gly	Gly	Gln		
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Ala	Leu	Ser	Thr	Leu	Glu	Cys	Val	Lys	Pro	Tyr	Leu	Glu	Gly	Ser	Asp		
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Cys	Ile	Ala	Gly	Val	Thr	Val	Pro	Ser	Thr	Arg	Glu	Val	Met	Ser	Leu		
	1875					1880					1885						
His	Glu	Ala	Ser	Arg	Lys	Glu	Leu	Ile	Pro	Ala	Ala	Phe	Ala	Thr	Trp		
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Leu	Leu	Glu	Ala	Gln	Ala	Ala	Thr	Gly	Phe	Leu	Leu	Asp	Pro	Cys	Thr		
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Arg	Gln	Lys	Leu	Ser	Val	Asp	Glu	Ala	Val	Asp	Val	Gly	Leu	Val	Asn		
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Glu	Glu	Leu	Arg	Glu	Arg	Leu	Leu	Lys	Ala	Glu	Arg	Ala	Ala	Thr	Gly		
	1940					1945					1950						
Tyr	Arg	Asp	Pro	Ala	Thr	Gly	Asp	Thr	Ile	Pro	Leu	Phe	Gln	Ala	Met		
	1955					1960					1965						
Gln	Lys	Gln	Leu	Ile	Glu	Lys	Ala	Glu	Ala	Leu	Arg	Leu	Leu	Glu	Val		
	1970					1975					1980						
Gln	Val	Ala	Thr	Gly	Gly	Val	Ile	Asp	Pro	Gln	His	His	His	Arg	Leu		
1985				1990					1995					2000			
Pro	Leu	Glu	Thr	Ala	Tyr	Arg	Arg	Gly	Cys	Leu	His	Lys	Asp	Ile	Tyr		
			2005					2010					2015				
Ala	Leu	Ile	Ser	Asp	Gln	Lys	His	Met	Arg	Lys	Arg	Phe	Val	Asp	Pro		
	2020					2025					2030						
Asn	Thr	Gln	Glu	Lys	Val	Ser	Tyr</										

Leu Trp Ala Leu Leu Asn Ser Glu Tyr Val Thr Glu Glu Lys Lys Leu  
 2100 2105 2110  
 Gln Leu Val Arg Met Tyr Arg Thr His Thr Arg Arg Ala Leu Gln Thr  
 2115 2120 2125  
 Val Ala Gln Leu Ile Leu Glu Leu Ile Glu Lys Gln Glu Thr Ser Asn  
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 Lys His Leu Trp Phe Gln Gly Ile Arg Arg Gln Ile Thr Ala Ser Glu  
 2145 2150 2155 2160  
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 2180 2185 2190  
 Arg Tyr Leu Glu Gly Thr Ser Cys Ile Ala Gly Val Leu Val Pro Ala  
 2195 2200 2205  
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 2210 2215 2220  
 Trp Lys Gly Val Leu Arg Pro Gly Thr Ala Leu Val Leu Leu Glu Ala  
 2225 2230 2235 2240  
 Gln Ala Ala Thr Gly Phe Val Ile Asp Pro Val Arg Asn Leu Arg Leu  
 2245 2250 2255  
 Ser Val Glu Glu Pro Val Pro Ala Gly Val Val Gly Ser Glu Ile Gln  
 2260 2265 2270  
 Glu Lys Leu Leu Ser Ala Glu Arg Ala Val Thr Gly Tyr Thr Asp Pro  
 2275 2280 2285  
 Tyr Thr Gly Gln Gln Ile Ser Leu Phe Gln Ala Met Gln Lys Asp Leu  
 2290 2295 2300  
 Ile Val Arg Glu His Gly Ile Arg Leu Leu Glu Ala Gln Ile Ala Thr  
 2305 2310 2315 2320  
 Gly Gly Val Ile Asp Pro Val His Ser His Arg Val Pro Val Asp Val  
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 Glu Val Ser Glu Asp Arg Arg Gln Asp Leu Leu Ser Arg Tyr Arg Ala

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Ala Gln Ala Gln	Ala Gln Ala Arg	Ala Glu Ala Glu	Ala Gly Ser Pro			
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Arg Pro Asp Pro	Arg Glu Ala Leu Arg	Ala Ala Thr Met	Glu Val Lys			
	3555	3560	3565			
Val Gly Arg Leu	Arg Gly Arg Ala	Val Pro Val Trp	Asp Val Leu Ala			
	3570	3575	3580			
Ser Gly Tyr Val	Ser Gly Ala Ala	Arg Glu Glu Leu	Ala Glu Phe			
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Gly Ser Gly Thr	Leu Asp Leu Pro	Ala Leu Thr Arg	Arg Leu Thr Ala			
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Ile Ile Glu Glu	Ala Glu Glu Ala	Pro Gly Ala Arg	Pro Gln Leu Gln			
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Asp Ala Trp Arg	Gly Pro Arg Glu	Pro Gly Pro Ala	Gly Arg Gly Asp			
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Gly Asp Ser Gly	Arg Ser Gln Arg	Glu Gly Gln Gly	Glu Gly Glu Thr			
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Gln Glu Ala Ala	Ala Ala Ala Ala	Ala Ala Arg Arg	Gln Glu Gln Thr			
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Leu Arg Asp Ala	Thr Met Glu Val	Gln Arg Gly Gln	Phe Gln Gly Arg			
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Pro Val Ser Val	Trp Asp Val Leu	Phe Ser Ser Tyr	Leu Ser Glu Ala			
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Arg Arg Asp Glu	Leu Leu Ala Gln	His Ala Ala Gly	Ala Leu Gly Leu			
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Pro Asp Leu Val	Ala Val Leu Thr	Arg Val Ile Glu	Glu Thr Glu Glu			
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Leu Ala Asp Pro	Ser Asp Asp Thr	Lys Gly Phe Phe	Asp Pro Asn Thr			
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His Glu Asn Leu	Thr Tyr Val Gln	Leu Leu Arg Arg	Cys Val Pro Asp			
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 Val His Gln Leu Ser Glu Glu Leu Arg Cys Ala Leu Arg Asp Ala Arg  
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Thr Glu Phe Pro Glu Leu Ala Pro Ser Gln Asn Gln Asn His Leu Lys
          35          40          45
Asp Trp Phe Leu Glu Asn Lys Ser Glu Val Cys Glu Cys Arg Asn Asn
          50          55          60
Glu Asp Gly Pro Gly Leu Ile Met Glu Glu Gln His Lys Cys Ser Ser
          65          70          75          80
Lys Ser Leu Glu His Lys Thr Gln Thr Pro Pro Val Glu Glu Asn Val
          85          90          95
Thr Gln Lys Ile Ser Asp Leu Glu Ile Cys Ala Asp Glu Phe Pro Gly
          100          105          110
Ser Ser Ala Thr Tyr Arg Ile Leu Glu Val Gly Cys Gly Val Gly Asn
          115          120          125
Thr Val Phe Pro Ile Leu Gln Thr Asn Asn Asp Pro Gly Leu Phe Val
          130          135          140
Tyr Cys Cys Asp Phe Ser Ser Thr Ala Ile Glu Leu Val Gln Thr Asn
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Ser Glu Tyr Asp Pro Ser Arg Cys Phe Ala Phe Val His Asp Leu Cys
          165          170          175
Asp Glu Glu Lys Ser Tyr Pro Val Pro Lys Gly Ser Leu Asp Ile Ile
          180          185          190
Ile Leu Ile Phe Val Leu Ser Ala Ile Val Pro Asp Lys Met Gln Lys
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Ala Ile Asn Arg Leu Ser Arg Leu Leu Lys Pro Gly Gly Met Val Leu
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          225          230          235          240
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          245          250          255
Val Tyr Phe Phe Thr Gln Glu Glu Leu Asp Thr Leu Phe Thr Thr Ala
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Gly Leu Glu Lys Val Gln Asn Leu Val Asp Arg Arg Leu Gln Val Asn
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Arg Gly Lys Gln Leu Thr Met Tyr Arg Val Trp Ile Gln Cys Lys Tyr
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Cys Lys Pro Leu Leu Ser Ser Thr Ser
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&lt;210&gt; 55

&lt;211&gt; 3334

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 55

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 <211> 509  
 <212> PRT  
 <213> Homo sapiens

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 Arg Lys Ser Val Val His Cys Ser Lys Ile Trp Ser Cys Arg Lys Arg





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 <211> 1760  
 <212> DNA  
 <213> Homo sapiens

<400> 57  
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<210> 58  
 <211> 232  
 <212> PRT  
 <213> Homo sapiens

<400> 58  
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 35 40 45  
 Leu Glu Ser Ser Asp Cys Glu Ser Leu Asp Ser Ser Asn Ser Gly Phe  
 50 55 60  
 Gly Pro Glu Glu Asp Thr Ala Tyr Leu Asp Gly Val Ser Leu Pro Asp  
 65 70 75 80  
 Phe Glu Leu Leu Ser Asp Pro Glu Asp Glu His Leu Cys Ala Asn Leu  
 85 90 95  
 Met Gln Leu Leu Gln Glu Ser Leu Ala Gln Ala Arg Leu Gly Ser Arg  
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Leu	Val	Leu	Arg	Leu	Asp	Ser	Arg	Leu	Trp	Pro	Lys	Ile	Gln	Gly	Leu
		180						185					190		
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&lt;210&gt; 59

&lt;211&gt; 2012

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 59

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 <211> 495  
 <212> PRT  
 <213> Homo sapiens

<400> 60

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Thr Gly Asp Met Gly Ser Leu Asp Asp Pro Lys Met Lys Ser Met Met					
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Pro Thr Asp Glu Gln Phe Ala Ala Ile Ile Val Leu Gly Phe Ala Thr					
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 <212> DNA  
 <213> Homo sapiens

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 atcgccctaa aggactggca ttcactgatg tggatgtcga ttccatcaaa attgcttggg 180  
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&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 62

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Trp	Lys	Cys	Glu	Arg	His	Thr	Ser	Val	Gln	Thr	Thr	Ser	Ser	Gly	Ser
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Pro	Gln	Pro	Pro	Pro	Tyr	Gly	His	Cys	Val	Thr	Asp	Ser	Gly	Val	Val
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Phe	Cys	Pro	Met	Ala	Ala	His	Glu	Glu	Ile	Cys	Thr	Thr	Asn	Glu	Gly
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Val	Met	Tyr	Arg	Ile	Gly	Asp	Gln	Trp	Asp	Lys	Gln	His	Asp	Met	Gly
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Cys	Ile	Ala	Tyr	Ser	Gln	Leu	Arg	Asp	Gln	Cys	Ile	Val	Asp	Asp	Ile
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 Ile Thr Val Tyr Ala Val Thr Gly Arg Gly Asp Ser Pro Ala Ser Ser  
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&lt;213&gt; Homo sapiens

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&lt;222&gt; 779

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 68

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<210> 69

<211> 756

<212> PRT

<213> Homo sapiens

<400> 69

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Val	Lys	Ala	Val	Ser	Trp	Leu	Cys	Val	Gly	Lys	Cys	Ser	Gly	Ser	Thr
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Lys	Val	Leu	Phe	Tyr	Arg	Trp	Leu	Val	Ala	Met	Phe	Asp	Phe	Ile	Asp
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Gln	Asp	Asp	Ala	Leu	Cys	Pro	Tyr	Val	Cys	His	Leu	Leu	Tyr	Leu	Leu
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Glu	Cys	Gly	Lys	Lys	Glu	Met	Ser	Leu	Ser	Asp	Cys	Leu	Asn	Arg	Ser
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&lt;210&gt; 71

&lt;211&gt; 338

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 71

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165          170          175
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195          200          205
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Asn	Leu	Ala	Glu	Ala	Leu	Ala	Ile	Leu	His	Cys	Val	Ala	Thr	Pro	Leu
			290			295					300				
Leu	Leu	Ala	Leu	Phe	Cys	His	Gln	Ala	Thr	Arg	Thr	Leu	Leu	Pro	Ser
					310					315					320
Leu	Pro	Leu	Pro	Glu	Gly	Trp	Ser	Ser	His	Leu	Asp	Thr	Leu	Gly	Ser
				325					330					335	
Lys	Ser														

<210> 72  
 <211> 817  
 <212> DNA  
 <213> Homo sapiens

<400> 72  
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 cgggtatcgct tttcttgtgc tacctgctgc tcttcacttg cagtggggtg gaggcaggta 180  
 agaaaaagtg ctcggagagc tcggacagcg gctccgggtt ctggaaggcc ctgaccttca 240  
 tggccgctcg aggaggactc gcagtcgccg ggctgcccgc gctgggcttc accggcgccg 300  
 gcatcgcggc caactcggtg gctgcctcgc tgatgagctg gtctgcgatc ctgaatgggg 360  
 gcggcggtgcc cgccgggggg ctagtggcca cgctgcagag cctcggggct ggtggcagca 420  
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 gtgaggagga tgaggagtag ccagcagctc ccagaacctc ttcttccttc ttggcctaac 540  
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 gttctcacta tattgtccag gctagagtgc agtggtatt cacagatgcg aacatagtag 660  
 actgcagcct ccaactccta gcctcaagtg atcctcctgt ctcaacctcc caagtaggat 720  
 tacaagcatg cgccgacgat gcccagaatc cagaactttg tctatcactc tccccaacaa 780  
 cctagatgtg aaaacagaat aaacttcacc cagaaaa 817

<210> 73  
 <211> 130  
 <212> PRT  
 <213> Homo sapiens

<400> 73  
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 Asp Ser Gly Ser Gly Phe Trp Lys Ala Leu Thr Phe Met Ala Val Gly  
 35 40 45  
 Gly Gly Leu Ala Val Ala Gly Leu Pro Ala Leu Gly Phe Thr Gly Ala  
 50 55 60  
 Gly Ile Ala Ala Asn Ser Val Ala Ala Ser Leu Met Ser Trp Ser Ala  
 65 70 75 80  
 Ile Leu Asn Gly Gly Gly Val Pro Ala Gly Gly Leu Val Ala Thr Leu  
 85 90 95  
 Gln Ser Leu Gly Ala Gly Gly Ser Ser Val Val Ile Gly Asn Ile Gly  
 100 105 110  
 Ala Leu Met Gly Tyr Ala Thr His Lys Tyr Leu Asp Ser Glu Glu Asp  
 115 120 125

Glu Glu  
130

<210> 74  
<211> 2861  
<212> DNA  
<213> Homo sapiens

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<210> 75  
 <211> 187  
 <212> PRT  
 <213> Homo sapiens

<400> 75

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      20           25           30
Val Glu Lys Leu Glu Thr Leu Asp Lys Asn Asn Val Leu Ala Ile Arg
      35           40           45
Arg Glu Ile Val Ala Leu Lys Thr Lys Leu Lys Glu Cys Glu Ala Ser
      50           55           60
Lys Asp Gln Asn Thr Pro Val Val His Pro Pro Thr Pro Gly Ser
65           70           75           80
Cys Gly His Gly Gly Val Val Asn Ile Ser Lys Pro Ser Val Val Gln
      85           90           95
Leu Asn Trp Arg Gly Phe Ser Tyr Leu Tyr Gly Ala Trp Gly Arg Asp
      100          105          110
Tyr Ser Pro Gln His Pro Asn Lys Gly Leu Tyr Trp Val Ala Pro Leu
      115          120          125
Asn Thr Asp Gly Arg Leu Leu Glu Tyr Tyr Ile Leu Tyr Asn Thr Leu
      130          135          140
Asp Asp Leu Leu Leu Tyr Ile Asn Ala Arg Glu Leu Arg Ile Thr Tyr
145          150          155          160
Gly Gln Gly Ser Gly Thr Ala Val Tyr Asn Asn Asn Met Tyr Val Asn
      165          170          175
Met Tyr Thr Pro Gly Ile Leu Pro Glu Leu Thr
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<210> 76  
 <211> 956  
 <212> DNA  
 <213> Homo sapiens

<400> 76

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<210> 77  
 <211> 266  
 <212> PRT  
 <213> Homo sapiens



&lt;400&gt; 77

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           20           25           30
Leu Ala Arg Ala Asp Leu Glu Met Gln Ile Glu Asn Leu Lys Glu Glu
 35           40           45
Leu Ala Tyr Leu Lys Lys Asn His Glu Glu Glu Met Asn Ala Leu Arg
 50           55           60
Gly Gln Val Gly Gly Glu Ile Asn Val Glu Met Asp Ala Ala Pro Gly
 65           70           75           80
Val Asp Leu Ser Arg Ile Leu Asn Glu Met Arg Asp Gln Tyr Glu Lys
           85           90           95
Met Ala Glu Lys Asn Arg Lys Asp Ala Glu Asp Trp Phe Phe Ser Lys
           100          105          110
Thr Glu Glu Leu Asn Arg Glu Val Ala Thr Asn Ser Glu Leu Val Gln
           115          120          125
Ser Gly Lys Ser Glu Ile Ser Glu Leu Arg Arg Thr Met Gln Ala Leu
           130          135          140
Glu Ile Glu Leu Gln Ser Gln Leu Ser Met Lys Ala Ser Leu Glu Gly
 145           150           155           160
Asn Leu Ala Glu Thr Glu Asn Arg Tyr Cys Val Gln Leu Ser Gln Ile
           165          170          175
Gln Gly Leu Ile Gly Ser Val Glu Glu Gln Leu Ala Gln Leu Arg Cys
           180          185          190
Glu Met Glu Gln Gln Asn Gln Glu Tyr Lys Ile Leu Leu Asp Val Lys
           195          200          205
Thr Arg Leu Glu Gln Glu Ile Ala Thr Tyr Arg Arg Leu Leu Glu Gly
           210          215          220
Glu Asp Ala His Leu Thr Gln Tyr Lys Lys Glu Pro Val Thr Thr Arg
 225           230           235           240
Gln Val Arg Thr Ile Val Glu Glu Val Gln Asp Gly Lys Val Ile Ser
           245          250          255
Ser Arg Glu Gln Val His Gln Thr Thr Arg
           260          265

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&lt;210&gt; 78

&lt;211&gt; 1689

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 78

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<210> 79  
 <211> 373  
 <212> PRT  
 <213> Homo sapiens

<400> 79

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			20					25					30		
Ile	Ser	Ile	Thr	Glu	Asn	Val	Leu	His	Phe	Lys	Ala	Gln	Gly	His	Gly
			35				40					45			
Ala	Lys	Gly	Asp	Asn	Val	Tyr	Glu	Phe	His	Leu	Glu	Phe	Leu	Asp	Leu
	50					55					60				
Val	Lys	Pro	Glu	Pro	Val	Tyr	Lys	Leu	Thr	Gln	Arg	Gln	Val	Asn	Ile
65					70					75				80	
Thr	Val	Gln	Lys	Lys	Val	Ser	Gln	Trp	Trp	Glu	Arg	Leu	Thr	Lys	Gln
			85					90						95	
Glu	Lys	Arg	Pro	Leu	Phe	Leu	Ala	Pro	Asp	Phe	Asp	Arg	Trp	Leu	Asp
			100					105					110		
Glu	Ser	Asp	Ala	Glu	Met	Glu	Leu	Arg	Ala	Lys	Glu	Glu	Glu	Arg	Leu
			115				120					125			
Asn	Lys	Leu	Arg	Leu	Glu	Ser	Glu	Gly	Ser	Pro	Glu	Thr	Leu	Thr	Asn
			130				135				140				
Leu	Arg	Lys	Gly	Tyr	Leu	Phe	Met	Tyr	Asn	Leu	Val	Gln	Phe	Leu	Gly
145					150					155					160
Phe	Ser	Trp	Ile	Phe	Val	Asn	Leu	Thr	Val	Arg	Phe	Cys	Ile	Leu	Gly
			165					170						175	
Lys	Glu	Ser	Phe	Tyr	Asp	Thr	Phe	His	Thr	Val	Ala	Asp	Met	Met	Tyr
			180					185					190		
Phe	Cys	Gln	Met	Leu	Ala	Val	Val	Glu	Thr	Ile	Asn	Ala	Ala	Ile	Gly
			195				200					205			
Val	Thr	Thr	Ser	Pro	Val	Leu	Pro	Ser	Leu	Ile	Gln	Leu	Leu	Gly	Arg
			210				215				220				
Asn	Phe	Ile	Leu	Phe	Ile	Ile	Phe	Gly	Thr	Met	Glu	Glu	Met	Gln	Asn
225					230					235					240
Lys	Ala	Val	Val	Phe	Phe	Val	Phe	Tyr	Leu	Trp	Ser	Ala	Ile	Glu	Ile
				245					250					255	
Phe	Arg	Tyr	Ser	Phe	Tyr	Met	Leu	Thr	Cys	Ile	Asp	Met	Asp	Trp	Lys
			260					265					270		
Val	Leu	Thr	Trp	Leu	Arg	Tyr	Thr	Leu	Trp	Ile	Pro	Leu	Tyr	Pro	Leu
			275				280					285			
Gly	Cys	Leu	Val	Glu	Ala	Val	Ser	Val	Ile	Gln	Ser	Ile	Pro	Ile	Phe
			290				295				300				

Asn Glu Thr Gly Arg Phe Ser Phe Thr Leu Pro Tyr Pro Val Lys Ile  
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 Lys Val Arg Phe Ser Phe Phe Leu Gln Ile Tyr Leu Ile Met Ile Phe  
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 Leu Gly Leu Tyr Ile Asn Phe Arg His Leu Tyr Lys Gln Arg Arg Arg  
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 Arg Tyr Gly Lys Lys Arg Lys Arg Ser Thr Lys Lys Lys Asp Leu Asp  
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 Gly Phe Leu Pro Val  
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<210> 80  
 <211> 1824  
 <212> DNA  
 <213> Homo sapiens

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 <211> 142  
 <212> PRT  
 <213> Homo sapiens

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<210> 82
<211> 10174
<212> DNA
<213> Homo sapiens
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<400> 82									
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&lt;210&gt; 83

&lt;211&gt; 2701

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 83

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35          40          45
Gly Ile Ser Arg Arg Met Pro Pro Ala Asn Leu Pro Ser Leu Lys
50          55          60
Ala Glu Asn Lys Gly Asn Asp Pro Asn Val Asn Ile Val Pro Lys Asp
65          70          75          80
Gly Thr Gly Trp Ala Ser Lys Gln Glu Gln His Glu Glu Glu Lys Thr
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Pro Glu Val Pro Pro Ala Gln Pro Lys Pro Gly Val Ala Ala Pro Pro
100          105          110
Glu Val Ala Pro Ala Pro Lys Ser Trp Ala Ser Asn Lys Gln Gly Gly
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Gln Gly Asp Gly Ile Gln Val Asn Ser Gln Phe Gln Gln Glu Phe Pro
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Cys Trp Arg Asp Gly Gly Lys Ala Ala Gly Ser Pro Ser Ser Ser Asp
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Gln Asp Glu Lys Leu Pro Gly Gln Asp Glu Ser Thr Ala Gly Thr Ser
195          200          205
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210          215          220
Pro Pro Gln Ala Lys Leu Asn Gly Gln Gln Ala Ala Leu Ala Ser Gln
225          230          235          240
Tyr Arg Ala Met Met Pro Pro Tyr Met Phe Gln Gln Tyr Pro Arg Met
245          250          255
Thr Tyr Pro Pro Leu His Gly Pro Met Arg Phe Pro Pro Ser Leu Ser
260          265          270
Glu Thr Asn Lys Gly Leu Arg Gly Arg Gly Pro Pro Pro Ser Trp Ala
275          280          285

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Pro	Met	Val	Glu	Lys	Gln	Glu	Ser	Glu	Asn	Ser	Cys	Asn	Lys	Glu	Glu
		610				615					620				
Glu	Pro	Val	Phe	Thr	Arg	Gln	Asp	Ser	Asn	Arg	Ser	Glu	Lys	Glu	Ala
625					630					635					640
Thr	Pro	Val	Val	His	Glu	Thr	Glu	Pro	Glu	Ser	Gly	Ser	Gln	Pro	Arg
				645					650					655	
Pro	Ala	Val	Leu	Ser	Gly	Tyr	Phe	Lys	Gln	Phe	Gln	Lys	Ser	Leu	Pro
			660					665					670		
Pro	Arg	Phe	Gln	Arg	Gln	Gln	Glu	Gln	Met	Lys	Gln	Gln	Gln	Trp	Gln
		675					680					685			
Gln	Gln	Gln	Gln	Gln	Gly	Val	Leu	Pro	Gln	Thr	Val	Pro	Ser	Gln	Pro
					695						700				
Ser	Ser	Ser	Thr	Val	Pro	Pro	Pro	Pro	His	Arg	Pro	Leu	Tyr	Gln	Pro
705					710					715					720
Met	Gln	Pro	His	Pro	Gln	His	Leu	Ala	Ser	Met	Gly	Phe	Asp	Pro	Arg
				725					730					735	
Trp	Leu	Met	Met	Gln	Ser	Tyr	Met	Asp	Pro	Arg	Met	Met	Ser	Gly	Arg
			740					745					750		
Pro	Ala	Met	Asp	Ile	Pro	Pro	Ile	His	Pro	Gly	Met	Ile	Pro	Pro	Lys



755	760	765
Pro Leu Met Arg Arg Asp	Gln Met Glu Gly Ser	Pro Asn Ser Ser Glu
770	775	780
Ser Phe Glu His Ile Ala	Arg Ser Ala Arg Asp	His Ala Ile Ser Leu
785	790	795
Ser Glu Pro Arg Met Leu	Trp Gly Ser Asp Pro	Tyr Pro His Ala Glu
805	810	815
Pro Gln Gln Ala Thr Thr	Pro Lys Ala Thr Glu	Glu Glu Pro Glu Asp Val
820	825	830
Arg Ser Glu Ala Ala Leu	Asp Gln Glu Gln Ile Thr	Ala Ala Tyr Ser
835	840	845
Val Glu His Asn Gln Leu	Glu Ala His Pro Lys	Ala Asp Phe Ile Arg
850	855	860
Glu Ser Ser Glu Ala Gln	Val Gln Lys Phe Leu	Ser Arg Ser Val Glu
865	870	875
Asp Val Arg Pro His His	Thr Asp Ala Asn Asn	Gln Ser Ala Cys Phe
885	890	895
Glu Ala Pro Asp Gln Lys	Thr Leu Ser Ala Pro	Gln Glu Glu Arg Ile
900	905	910
Ser Ala Val Glu Ser Gln	Pro Ser Arg Lys Arg	Ser Val Ser His Gly
915	920	925
Ser Asn His Thr Gln Lys	Pro Asp Glu Gln Arg	Ser Glu Pro Ser Ala
930	935	940
Gly Ile Pro Lys Val Thr	Ser Arg Cys Ile Asp	Ser Lys Glu Pro Ile
945	950	955
Glu Arg Pro Glu Glu Lys	Pro Lys Lys Glu Gly	Phe Ile Arg Ser Ser
965	970	975
Glu Gly Pro Lys Pro Glu	Lys Val Tyr Lys Ser	Lys Ser Glu Thr Arg
980	985	990
Trp Gly Pro Arg Pro Ser	Ser Asn Arg Arg Glu	Glu Val Asn Asp Arg
995	1000	1005
Pro Val Arg Arg Ser Gly	Pro Ile Lys Lys Pro	Val Leu Arg Asp Met
1010	1015	1020
Lys Glu Glu Arg Glu Gln	Arg Lys Glu Lys Glu	Gly Glu Lys Ala Glu
1025	1030	1035
Lys Val Thr Glu Lys Val	Val Val Lys Pro Glu	Lys Thr Glu Lys Lys
1045	1050	1055
Asp Leu Pro Pro Pro Pro	Pro Pro Pro Gln Pro	Pro Ala Pro Ile Gln
1060	1065	1070
Pro Gln Ser Val Pro Pro	Pro Ile Gln Pro Glu	Ala Glu Lys Phe Pro
1075	1080	1085
Ser Thr Glu Thr Ala Thr	Leu Ala Gln Lys Pro	Ser Gln Asp Thr Glu
1090	1095	1100
Lys Pro Leu Glu Pro Val	Ser Thr Val Gln Val	Glu Pro Ala Val Lys
1105	1110	1115
Thr Val Asn Gln Gln Thr	Met Ala Ala Pro Val	Val Lys Glu Glu Lys
1125	1130	1135
Gln Pro Glu Lys Val Ile	Ser Lys Asp Leu Val	Ile Glu Arg Pro Arg
1140	1145	1150
Pro Asp Ser Arg Pro Ala	Val Lys Lys Glu Ser	Thr Leu Pro Pro Arg
1155	1160	1165
Thr Tyr Trp Lys Glu Ala	Arg Glu Arg Asp Trp	Phe Pro Asp Gln Gly
1170	1175	1180
Tyr Arg Gly Arg Gly Arg	Gly Glu Tyr Tyr Ser	Arg Gly Arg Ser Tyr
1185	1190	1195
Arg Gly Ser Tyr Gly Gly	Arg Gly Arg Gly His	Thr Arg
1205	1210	1215
Asp Tyr Pro Gln Tyr Arg	Asp Asn Lys Pro Arg	Ala Glu His Ile Pro
1220	1225	1230

Ser Gly Pro Leu Arg Gln Arg Glu Glu Ser Glu Thr Arg Ser Glu Ser  
 1235 1240 1245  
 Ser Asp Phe Glu Val Val Pro Lys Arg Arg Arg Gln Arg Gly Ser Glu  
 1250 1255 1260  
 Thr Asp Thr Asp Ser Glu Ile His Glu Ser Ala Ser Asp Lys Asp Ser  
 1265 1270 1275 1280  
 Leu Ser Lys Gly Lys Leu Pro Lys Arg Glu Glu Arg Pro Glu Asn Lys  
 1285 1290 1295  
 Lys Pro Val Lys Pro His Ser Ser Phe Lys Pro Asp Asn His Val Arg  
 1300 1305 1310  
 Ile Asp Asn Arg Leu Leu Glu Lys Pro Tyr Val Arg Asp Asp Asp Lys  
 1315 1320 1325  
 Ala Lys Pro Gly Phe Leu Pro Lys Gly Glu Pro Thr Arg Arg Gly Arg  
 1330 1335 1340  
 Gly Gly Thr Phe Arg Arg Gly Gly Arg Asp Pro Gly Gly Arg Pro Ser  
 1345 1350 1355 1360  
 Arg Pro Ser Thr Leu Arg Arg Pro Ala Tyr Arg Asp Asn Gln Trp Asn  
 1365 1370 1375  
 Pro Arg Gln Ser Glu Val Pro Lys Pro Glu Asp Gly Glu Pro Pro Arg  
 1380 1385 1390  
 Arg His Glu Gln Phe Ile Pro Ile Ala Ala Asp Lys Arg Pro Pro Lys  
 1395 1400 1405  
 Phe Glu Arg Lys Phe Asp Pro Ala Arg Glu Arg Pro Arg Arg Gln Arg  
 1410 1415 1420  
 Pro Thr Arg Pro Pro Arg Gln Asp Lys Pro Pro Arg Phe Arg Arg Leu  
 1425 1430 1435 1440  
 Arg Glu Arg Glu Ala Ala Ser Lys Ser Asn Glu Val Val Ala Val Pro  
 1445 1450 1455  
 Thr Asn Gly Thr Val Asn Asn Val Ala Gln Glu Pro Val Asn Thr Leu  
 1460 1465 1470  
 Gly Asp Ile Ser Gly Asn Lys Thr Pro Asp Leu Ser Asn Gln Asn Ser  
 1475 1480 1485  
 Ser Asp Gln Ala Asn Glu Glu Trp Glu Thr Ala Ser Glu Ser Ser Asp  
 1490 1495 1500  
 Phe Asn Glu Arg Arg Glu Arg Asp Glu Lys Lys Asn Ala Asp Leu Asn  
 1505 1510 1515 1520  
 Ala Gln Thr Val Val Lys Val Gly Glu Asn Val Leu Pro Pro Lys Arg  
 1525 1530 1535  
 Glu Ile Ala Lys Arg Ser Phe Ser Ser Gln Arg Pro Val Asp Arg Gln  
 1540 1545 1550  
 Asn Arg Arg Gly Asn Asn Gly Pro Pro Lys Ser Gly Arg Asn Phe Ser  
 1555 1560 1565  
 Gly Pro Arg Asn Glu Arg Arg Ser Gly Pro Pro Ser Lys Ser Gly Lys  
 1570 1575 1580  
 Arg Gly Pro Phe Asp Asp Gln Pro Ala Gly Thr Thr Gly Val Asp Leu  
 1585 1590 1595 1600  
 Ile Asn Gly Ser Ser Ala His His Gln Glu Gly Val Pro Asn Gly Thr  
 1605 1610 1615  
 Gly Gln Lys Asn Ser Lys Asp Ser Thr Gly Lys Lys Arg Glu Asp Pro  
 1620 1625 1630  
 Lys Pro Gly Pro Lys Lys Pro Lys Glu Lys Val Asp Ala Leu Ser Gln  
 1635 1640 1645  
 Phe Asp Leu Asn Asn Tyr Ala Ser Val Val Ile Ile Asp Asp His Pro  
 1650 1655 1660  
 Glu Val Thr Val Ile Glu Asp Pro Gln Ser Asn Leu Asn Asp Asp Gly  
 1665 1670 1675 1680  
 Phe Thr Glu Val Val Ser Lys Lys Gln Gln Lys Arg Leu Gln Asp Glu  
 1685 1690 1695  
 Glu Arg Arg Lys Lys Glu Glu Gln Val Ile Gln Val Trp Asn Lys Lys

[illegible]

Ala Glu Tyr Gly Thr Asn Ala Lys Glu Ser Val Thr Asp Tyr Thr Thr  
 2180 2185 2190  
 Pro Ser Ser Ser Leu Pro Asn Thr Val Ala Thr Asn Asn Thr Lys Met  
 2195 2200 2205  
 Glu Asp Thr Leu Val Asn Asn Val Pro Leu Pro Asn Thr Leu Pro Leu  
 2210 2215 2220  
 Pro Lys Arg Glu Thr Ile Gln Gln Ser Ser Ser Leu Thr Ser Val Pro  
 2225 2230 2235 2240  
 Pro Thr Thr Phe Ser Leu Thr Phe Lys Met Glu Ser Ala Arg Lys Ala  
 2245 2250 2255  
 Trp Glu Asn Ser Pro Asn Val Arg Glu Lys Gly Ser Pro Val Thr Ser  
 2260 2265 2270  
 Thr Ala Pro Pro Ile Ala Thr Gly Val Ser Ser Ser Ala Ser Gly Pro  
 2275 2280 2285  
 Ser Thr Ala Asn Tyr Asn Ser Phe Ser Ser Ala Ser Met Pro Gln Ile  
 2290 2295 2300  
 Pro Val Ala Ser Val Thr Pro Thr Ala Ser Leu Ser Gly Ala Gly Thr  
 2305 2310 2315 2320  
 Tyr Thr Thr Ser Ser Leu Ser Thr Lys Ser Thr Thr Thr Ser Asp Pro  
 2325 2330 2335  
 Pro Asn Ile Cys Lys Val Lys Pro Gln Gln Leu Gln Thr Ser Ser Leu  
 2340 2345 2350  
 Pro Ser Ala Ser His Phe Ser Gln Leu Ser Cys Met Pro Ser Leu Ile  
 2355 2360 2365  
 Ala Gln Gln Gln Gln Asn Pro Gln Val Tyr Val Ser Gln Ser Ala Ala  
 2370 2375 2380  
 Ala Gln Ile Pro Ala Phe Tyr Met Asp Thr Ser His Leu Phe Asn Thr  
 2385 2390 2395 2400  
 Gln His Ala Arg Leu Ala Pro Pro Ser Leu Ala Gln Gln Gln Gly Phe  
 2405 2410 2415  
 Gln Pro Gly Leu Ser Gln Pro Thr Ser Val Gln Gln Ile Pro Ile Pro  
 2420 2425 2430  
 Ile Tyr Ala Pro Leu Gln Gly Gln His Gln Ala Gln Leu Ser Leu Gly  
 2435 2440 2445  
 Ala Gly Pro Ala Val Ser Gln Ala Gln Glu Leu Phe Ser Ser Ser Leu  
 2450 2455 2460  
 Gln Pro Tyr Arg Ser Gln Pro Ala Phe Met Gln Ser Ser Leu Ser Gln  
 2465 2470 2475 2480  
 Pro Ser Val Val Leu Ser Gly Thr Ala Ile His Asn Phe Pro Thr Val  
 2485 2490 2495  
 Gln His Gln Glu Leu Ala Lys Ala Gln Ser Gly Leu Ala Phe Gln Gln  
 2500 2505 2510  
 Thr Ser Asn Thr Gln Pro Ile Pro Ile Leu Tyr Glu His Gln Leu Gly  
 2515 2520 2525  
 Gln Ala Ser Gly Leu Gly Gly Ser Gln Leu Ile Asp Thr His Leu Leu  
 2530 2535 2540  
 Gln Ala Arg Ala Asn Leu Thr Gln Ala Ser Asn Leu Tyr Ser Gly Gln  
 2545 2550 2555 2560  
 Val Gln Gln Pro Gly Gln Thr Asn Phe Tyr Asn Thr Ala Gln Ser Pro  
 2565 2570 2575  
 Ser Ala Leu Gln Gln Val Thr Val Pro Leu Pro Ala Ser Gln Leu Ser  
 2580 2585 2590  
 Leu Pro Asn Phe Gly Ser Thr Gly Gln Pro Leu Ile Ala Leu Pro Gln  
 2595 2600 2605  
 Thr Leu Gln Pro Pro Leu Gln His Thr Thr Pro Gln Ala Gln Ala Gln  
 2610 2615 2620  
 Ser Leu Ser Arg Pro Ala Gln Val Ser Gln Pro Phe Arg Gly Leu Ile  
 2625 2630 2635 2640  
 Pro Ala Gly Thr Gln His Ser Met Ile Ala Thr Thr Gly Lys Met Ser

	2645		2650		2655
Glu Met	Glu Lys Ala Phe Gly	Ser Gly Ile Asp Ile	Lys Pro Gly		
	2660	2665	2670		
Thr Pro	Pro Ile Ala Gly Arg Ser	Thr Thr Pro Thr Ser	Ser Pro Ser		
	2675	2680	2685		
Gly Leu	Leu Leu Gln Val Arg Thr	Ala Ser Pro Ala Lys			
	2690	2695	2700		

<210> 84  
 <211> 597  
 <212> DNA  
 <213> Homo sapiens

<400> 84  
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 ggctctgccc tagttttgcc cctggccagg attgctacag ttgtgattgg aggagttgtg 180  
 gccatggcgg ctgtgcccat ggtgctcagt gccatgggct tcaactgcgc ggggaatcgcc 240  
 tcgtcctcca tagcagccaa gatgatgtcc gcggcgccca ttgccaatgg ggggtggagtt 300  
 gcctcgggca gccttgtggg tactctgcag tcaactgggag caactggact ctccggattg 360  
 accaagttca tcctgggctc cattgggtct gccattgcgc ctgtcattgc gaggttctac 420  
 tagctccctg cccctcgccc tgcagagaag agaaccatgc cagggggagaa ggcacccagc 480  
 catcctgacc cagcgaggag ccaactatcc caaatatacc tgggtgaaat ataccaaatt 540  
 ctgcatctcc agaggaaaat aagaaataaa gatgaattgt tgcaactctt aaaaaaa 597

<210> 85  
 <211> 122  
 <212> PRT  
 <213> Homo sapiens

<400> 85  
 Met Glu Ala Ser Ala Leu Thr Ser Ser Ala Val Thr Ser Val Ala Lys  
 1 5 10 15  
 Val Val Arg Val Ala Ser Gly Ser Ala Val Val Leu Pro Leu Ala Arg  
 20 25 30  
 Ile Ala Thr Val Val Ile Gly Gly Val Val Ala Met Ala Ala Val Pro  
 35 40 45  
 Met Val Leu Ser Ala Met Gly Phe Thr Ala Ala Gly Ile Ala Ser Ser  
 50 55 60  
 Ser Ile Ala Ala Lys Met Met Ser Ala Ala Ala Ile Ala Asn Gly Gly  
 65 70 75 80  
 Gly Val Ala Ser Gly Ser Leu Val Gly Thr Leu Gln Ser Leu Gly Ala  
 85 90 95  
 Thr Gly Leu Ser Gly Leu Thr Lys Phe Ile Leu Gly Ser Ile Gly Ser  
 100 105 110  
 Ala Ile Ala Ala Val Ile Ala Arg Phe Tyr  
 115 120

<210> 86  
 <211> 1032  
 <212> DNA  
 <213> Homo sapiens

<400> 86  
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 tgcccctgct gcgatgacct tctcgccact tctgctgttc ctgccaccgc tgetgctgct 120  
 gctggacgtc cccacggcgg cgggtgcaggc gtcccctctg caagcgtag acttctttgg 180

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gaatgggcca ccagttaact acaagacagg caatctatac ctgcgggggc ccctgaagaa 240
gtccaatgca ccgcttgta atgtgaccct ctactatgaa gcactgtgcg gtggctgccg 300
agccttcctg atccgggagc tcttcccaac atggctgttg gtcattggaga tcctcaatgt 360
cacgtcgggtg ccctacggaa acgcacagga acaaaatgtc agtggcaggt gggagttcaa 420
gtgccagctt ggagaagagg agtgcaaatt caacaagggtg gaggcctgcg tgttgatga 480
acttgacatg gagctagcct tcctgaccat gtctggcatg gcatggaaga gtttgaggac 540
atggagagaa gtctgccact atgcctgcag ctctacgcc cagggctgtc gccagaacta 600
tcatggagtg tgcaatgggg gaccgcggca tgcagctcat gcacgccaac gccagcggga 660
cagatgctct ccagccaccg cagcagtatg tgccctgggt caccgtcaat gggaaaccct 720
tggaagatca gaccagctc cttacccttg tctgccagtt gtaccagggc aagaagccgg 780
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gctgcggaga gctcatggaa ggcgagtggg aactcggctg cctgcctttt tttctgatcc 900
agaccctcgg cacctgctac ttaccaactg gaaaatttta tgcattccat gaagcccaga 960
tacacaaaat tccacccta gatcaagaat cctgctccac taagaatggt gctaaagtaa 1020
aactagttta at 1032

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&lt;210&gt; 87

&lt;211&gt; 303

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 87

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Met Asp Ser Arg His Thr Phe Ala Pro Ala Ala Met Thr Leu Ser Pro
1          5          10          15
Leu Leu Leu Phe Leu Pro Pro Leu Leu Leu Leu Leu Asp Val Pro Thr
20          25          30
Ala Ala Val Gln Ala Ser Pro Leu Gln Ala Leu Asp Phe Phe Gly Asn
35          40          45
Gly Pro Pro Val Asn Tyr Lys Thr Gly Asn Leu Tyr Leu Arg Gly Pro
50          55          60
Leu Lys Lys Ser Asn Ala Pro Leu Val Asn Val Thr Leu Tyr Tyr Glu
65          70          75          80
Ala Leu Cys Gly Gly Cys Arg Ala Phe Leu Ile Arg Glu Leu Phe Pro
85          90          95
Thr Trp Leu Leu Val Met Glu Ile Leu Asn Val Thr Ser Val Pro Tyr
100          105          110
Gly Asn Ala Gln Glu Gln Asn Val Ser Gly Arg Trp Glu Phe Lys Cys
115          120          125
Gln Leu Gly Glu Glu Glu Cys Lys Phe Asn Lys Val Glu Ala Cys Val
130          135          140
Leu Asp Glu Leu Asp Met Glu Leu Ala Phe Leu Thr Met Ser Gly Met
145          150          155          160
Ala Trp Lys Ser Leu Arg Thr Trp Arg Glu Val Cys His Tyr Ala Cys
165          170          175
Ser Ser Thr Pro Gln Gly Cys Arg Gln Asn Tyr His Gly Val Cys Asn
180          185          190
Gly Gly Pro Arg His Ala Ala His Ala Arg Gln Arg Pro Ala Asp Arg
195          200          205
Cys Ser Pro Ala Thr Ala Arg Val Cys Ala Leu Gly His Arg Gln Trp
210          215          220
Glu Thr Leu Gly Arg Ser Asp Pro Ala Pro Tyr Pro Cys Leu Pro Val
225          230          235          240
Val Pro Gly Gln Glu Ala Gly Cys Leu Pro Phe Leu Asn Gln Leu Pro
245          250          255
Pro Glu Cys Leu Leu Arg Val Leu Ala Gly Gly Leu Arg Arg Ala His
260          265          270
Gly Arg Arg Val Gly Thr Arg Leu Pro Ala Phe Phe Ser Asp Pro Asp
275          280          285
Pro Arg His Leu Leu Leu Thr Asn Trp Lys Ile Leu Cys Ile Pro

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290

295

300

<210> 88  
 <211> 905  
 <212> DNA  
 <213> Homo sapiens

<400> 88  
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 taatttgatc ctcaggaatt tgttctgccc tcatctggcc ctggccagct ctgcatttga 180  
 caaatgccag gaagaggaaa ctggttgagaa aacggaaacta ctggggaaaag ggaggggtca 240  
 ctgagaacca tcccggtaac ccgaccgccc ctggtcacca tgaaccacat tgtgcaaacc 300  
 ttctctcctg tcaacagcgg ccagcctccc aactacgaga tgctcaagga ggagcaggaa 360  
 gtggctatgc tggggggggc ccacaaccct gctcccccca cgtccaccgt gatccacatc 420  
 cgcagcgaga cctccgtgcc tgaccatgtc gtctggtccc tgttcaaac cctcttcattg 480  
 aacacctgct gcctgggctt catagcattc gcctactcog tgaagtctag ggacaggaag 540  
 atggttgggc acgtgaccgg ggcccaggcc tatgcctcca ccgccaagt cctgaacatc 600  
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 gtccaggccc agcgatagat caggaggcat cattgaggcc aggagctctg cccgtgacct 720  
 gtatcccacg tactctatct tccattcctc gccctgcccc cagaggccag gagctctgcc 780  
 cttgacctgt attccactta ctccaccttc cattcctcgc cctgtcccca cagccgagtc 840  
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 tttct 905

<210> 89  
 <211> 132  
 <212> PRT  
 <213> Homo sapiens

<400> 89  
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 20 25 30  
 Gly Pro His Asn Pro Ala Pro Pro Thr Ser Thr Val Ile His Ile Arg  
 35 40 45  
 Ser Glu Thr Ser Val Pro Asp His Val Val Trp Ser Leu Phe Asn Thr  
 50 55 60  
 Leu Phe Met Asn Thr Cys Cys Leu Gly Phe Ile Ala Phe Ala Tyr Ser  
 65 70 75 80  
 Val Lys Ser Arg Asp Arg Lys Met Val Gly Asp Val Thr Gly Ala Gln  
 85 90 95  
 Ala Tyr Ala Ser Thr Ala Lys Cys Leu Asn Ile Trp Ala Leu Ile Leu  
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 Gly Ile Phe Met Thr Ile Leu Leu Val Ile Ile Pro Val Leu Val Val  
 115 120 125  
 Gln Ala Gln Arg  
 130

<210> 90  
 <211> 2499  
 <212> DNA  
 <213> Homo sapiens

<400> 90  
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tcttttcaact ttccagtagt cagcaaagag cagtttgaat tttcttgtcg cttcctatca 1260
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gaaggtctgg caaagtcagg ctcagggaga ctctgccctg ctgcagacct cggtgtggac 2340
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gcaatgtatt tataaatagt aaataaagtt tttaccatt 2499

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&lt;210&gt; 91

&lt;211&gt; 291

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 91

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Met Gln Arg Ala Arg Pro Thr Leu Trp Ala Ala Ala Leu Thr Leu Leu
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Val Leu Leu Arg Gly Pro Pro Val Ala Arg Ala Gly Ala Ser Ser Gly
      20             25             30
Gly Leu Gly Pro Val Val Arg Cys Glu Pro Cys Asp Ala Arg Ala Leu
      35             40             45
Ala Gln Cys Ala Pro Pro Pro Ala Val Cys Ala Glu Leu Val Arg Glu
      50             55             60
Pro Gly Cys Gly Cys Cys Leu Thr Cys Ala Leu Ser Glu Gly Gln Pro
      65             70             75             80
Cys Gly Ile Tyr Thr Glu Arg Cys Gly Ser Gly Leu Arg Cys Gln Pro

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[illegible]

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<210> 92
<211> 1639
<212> DNA
<213> Homo sapiens
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<400> 92							
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 <211> 99  
 <212> PRT  
 <213> Homo sapiens

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 Arg Cys Gln Cys Ile Lys Thr Tyr Ser Lys Pro Phe His Pro Lys Phe  
 35 40 45  
 Ile Lys Glu Leu Arg Val Ile Glu Ser Gly Pro His Cys Ala Asn Thr  
 50 55 60  
 Glu Ile Ile Val Lys Leu Ser Asp Gly Arg Glu Leu Cys Leu Asp Pro  
 65 70 75 80  
 Lys Glu Asn Trp Val Gln Arg Val Val Glu Lys Phe Leu Lys Arg Ala  
 85 90 95  
 Glu Asn Ser

<210> 94  
 <211> 1840  
 <212> DNA  
 <213> Homo sapiens

<400> 94  
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 catccgcctc ttccagcagc agaagcaccg gcagggcagc ttggacacag ggaagaggc 660  
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 tgagtgtccc agccatatag caggcacgtc cgggtcctca ctgtccttcc actcaacagt 1200  
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 gccaccaag ctgagaccca tgtccatggt gtactatgat gatggtcaaa acatcatcaa 1320  
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 gtttctgagt taaccagaaa aatagaaatt aaaaacaaaa caaaacaaaa aaaaaacaa 1500  
 aaaaaacaa aagtaaatta aaaacaaacc tgatgaaaca gatgaaacag atgaaggaag 1560

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&lt;210&gt; 95

&lt;211&gt; 426

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 95

```

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 20          25          30
Pro Asp Cys Pro Ser Cys Ala Leu Ala Leu Pro Lys Asp Val Pro
 35          40          45
Asn Ser Gln Pro Glu Met Val Glu Ala Val Lys Lys His Ile Leu Asn
 50          55          60
Met Leu His Leu Lys Lys Arg Pro Asp Val Thr Gln Pro Val Pro Lys
 65          70          75          80
Ala Ala Leu Leu Asn Ala Ile Arg Lys Leu His Val Gly Lys Val Gly
 85          90          95
Glu Asn Gly Tyr Val Glu Ile Glu Asp Asp Ile Gly Arg Arg Ala Glu
100          105          110
Met Asn Glu Leu Met Glu Gln Thr Ser Glu Ile Ile Thr Phe Ala Glu
115          120          125
Ser Gly Thr Ala Arg Lys Thr Leu His Phe Glu Ile Ser Lys Glu Gly
130          135          140
Ser Asp Leu Ser Val Val Glu Arg Ala Glu Val Trp Leu Phe Leu Lys
145          150          155          160
Val Pro Lys Ala Asn Arg Thr Arg Thr Lys Val Thr Ile Arg Leu Phe
165          170          175
Gln Gln Gln Lys His Pro Gln Gly Ser Leu Asp Thr Gly Glu Glu Ala
180          185          190
Glu Glu Val Gly Leu Lys Gly Glu Arg Ser Glu Leu Leu Leu Ser Glu
195          200          205
Lys Val Val Asp Ala Arg Lys Ser Thr Trp His Val Phe Pro Val Ser
210          215          220
Ser Ser Ile Gln Arg Leu Leu Asp Gln Gly Lys Ser Ser Leu Asp Val
225          230          235          240
Arg Ile Ala Cys Glu Gln Cys Gln Glu Ser Gly Ala Ser Leu Val Leu
245          250          255
Leu Gly Lys Lys Lys Lys Lys Glu Glu Glu Gly Glu Gly Lys Lys Lys
260          265          270
Gly Gly Gly Glu Gly Gly Ala Gly Ala Asp Glu Glu Lys Glu Gln Ser
275          280          285
His Arg Pro Phe Leu Met Leu Gln Ala Arg Gln Ser Glu Asp His Pro
290          295          300
His Arg Arg Arg Arg Arg Gly Leu Glu Cys Asp Gly Lys Val Asn Ile
305          310          315          320
Cys Cys Lys Lys Gln Phe Phe Val Ser Phe Lys Asp Ile Gly Trp Asn
325          330          335
Asp Trp Ile Ile Ala Pro Ser Gly Tyr His Ala Asn Tyr Cys Glu Gly
340          345          350
Glu Cys Pro Ser His Ile Ala Gly Thr Ser Gly Ser Ser Leu Ser Phe
355          360          365
His Ser Thr Val Ile Asn His Tyr Arg Met Arg Gly His Ser Pro Phe

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370	375	380
Ala Asn Leu Lys Ser Cys Cys Val Pro Thr Lys	Leu Arg Pro Met Ser	
385	390	395
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 <211> 4637  
 <212> DNA  
 <213> Homo sapiens

<400> 96  
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&lt;210&gt; 97

&lt;211&gt; 1051

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 97

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 20           25           30
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 35           40           45
Gly Ser Leu Phe Gly Tyr Ser Val Ala Leu His Arg Gln Thr Glu Arg
 50           55           60
Gln Gln Arg Tyr Leu Leu Leu Ala Gly Ala Pro Arg Glu Leu Ala Val
 65           70           75           80
Pro Asp Gly Tyr Thr Asn Arg Thr Gly Ala Val Tyr Leu Cys Pro Leu
 85           90           95
Thr Ala His Lys Asp Asp Cys Glu Arg Met Asn Ile Thr Val Lys Asn
100          105          110
Asp Pro Gly His His Ile Ile Glu Asp Met Trp Leu Gly Val Thr Val
115          120          125
Ala Ser Gln Gly Pro Ala Gly Arg Val Leu Val Cys Ala His Arg Tyr
130          135          140

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Lys	Cys	Tyr	Val	Arg	Gly	Asn	Asp	Leu	Glu	Leu	Asp	Ser	Ser	Asp	Asp
				165					170						175
Trp	Gln	Thr	Tyr	His	Asn	Glu	Met	Cys	Asn	Ser	Asn	Thr	Asp	Tyr	Leu
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Glu	Thr	Gly	Met	Cys	Gln	Leu	Gly	Thr	Ser	Gly	Gly	Phe	Thr	Gln	Asn
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Thr	Val	Tyr	Phe	Gly	Ala	Pro	Gly	Ala	Tyr	Asn	Trp	Lys	Gly	Asn	Ser
	210					215					220				
Tyr	Met	Ile	Gln	Arg	Lys	Glu	Trp	Asp	Leu	Ser	Glu	Tyr	Ser	Tyr	Lys
225					230					235					240
Asp	Pro	Glu	Asp	Gln	Gly	Asn	Leu	Tyr	Ile	Gly	Tyr	Thr	Met	Gln	Val
				245					250						255
Gly	Ser	Phe	Ile	Leu	His	Pro	Lys	Asn	Ile	Thr	Ile	Val	Thr	Gly	Ala
			260					265						270	
Pro	Arg	His	Arg	His	Met	Gly	Ala	Val	Phe	Leu	Leu	Ser	Gln	Glu	Ala
		275					280						285		
Gly	Gly	Asp	Leu	Arg	Arg	Arg	Gln	Val	Leu	Glu	Gly	Ser	Gln	Val	Gly
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Ala	Tyr	Phe	Gly	Ser	Ala	Ile	Ala	Leu	Ala	Asp	Leu	Asn	Asn	Asp	Gly
305					310					315					320
Trp	Gln	Asp	Leu	Leu	Val	Gly	Ala	Pro	Tyr	Tyr	Phe	Glu	Arg	Lys	Glu
				325					330					335	
Glu	Val	Gly	Gly	Ala	Ile	Tyr	Val	Phe	Met	Asn	Gln	Ala	Gly	Thr	Ser
			340					345					350		
Phe	Pro	Ala	His	Pro	Ser	Leu	Leu	Leu	His	Gly	Pro	Ser	Gly	Ser	Ala
		355					360					365			
Phe	Gly	Leu	Ser	Val	Ala	Ser	Ile	Gly	Asp	Ile	Asn	Gln	Asp	Gly	Phe
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Gln	Asp	Ile	Ala	Val	Gly	Ala	Pro	Phe	Glu	Gly	Leu	Gly	Lys	Val	Tyr
385					390					395					400
Ile	Tyr	His	Ser	Ser	Ser	Lys	Gly	Leu	Leu	Arg	Gln	Pro	Gln	Gln	Val
				405					410						415
Ile	His	Gly	Glu	Lys	Leu	Gly	Leu	Pro	Gly	Leu	Ala	Thr	Phe	Gly	Tyr
			420					425					430		
Ser	Leu	Ser	Gly	Gln	Met	Asp	Val	Asp	Glu	Asn	Phe	Tyr	Pro	Asp	Leu
		435					440					445			
Leu	Val	Gly	Ser	Leu	Ser	Asp	His	Ile	Val	Leu	Leu	Arg	Ala	Arg	Pro
	450					455					460				
Val	Ile	Asn	Ile	Val	His	Lys	Thr	Leu	Val	Pro	Arg	Pro	Ala	Val	Leu
465					470					475					480
Asp	Pro	Ala	Leu	Cys	Thr	Ala	Thr	Ser	Cys	Val	Gln	Val	Glu	Leu	Cys
			485						490					495	
Phe	Ala	Tyr	Asn	Gln	Ser	Ala	Gly	Asn	Pro	Asn	Tyr	Arg	Arg	Asn	Ile
			500					505					510		
Thr	Leu	Ala	Tyr	Thr	Leu	Glu	Ala	Asp	Arg	Asp	Arg	Arg	Pro	Pro	Arg
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Leu	Arg	Phe	Ala	Gly	Ser	Glu	Ser	Ala	Val	Phe	His	Gly	Phe	Phe	Ser
	530					535					540				
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Leu	Arg	Asp	Lys	Leu	Arg	Pro	Ile	Ile	Ile	Ser	Met	Asn	Tyr	Ser	Leu
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Pro	Leu	Arg	Met	Pro	Asp	Arg	Pro	Arg	Leu	Gly	Leu	Arg	Ser	Leu	Asp
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Arg Leu Gln Tyr Ser	Arg Asp Val Arg Lys Leu	Leu Leu Ser Ile Asn
645	650	655
Val Thr Asn Thr Arg	Thr Ser Glu Arg Ser Gly	Glu Asp Ala His Glu
660	665	670
Ala Leu Leu Thr Leu	Val Val Pro Pro Ala Leu	Leu Leu Ser Ser Val
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Arg Pro Pro Gly Ala	Cys Gln Ala Asn Glu Thr	Ile Phe Cys Glu Leu
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Glu Val Ile Gly Val	Thr Leu His Thr Arg Asp	Leu Gln Val Gln Leu
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Gln Leu Ser Thr Ser	Ser His Gln Asp Asn Leu	Trp Pro Met Ile Leu
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His Arg Leu Gln Ser	Phe Phe Gly Gly Thr Val	Met Gly Glu Ser Gly
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Asp Ile Asp Ser Glu	Leu Val Glu Glu Leu Pro	Ala Glu Ile Glu Leu
980	985	990
Trp Leu Val Leu Val	Ala Val Gly Ala Gly Leu	Leu Leu Leu Gly Leu
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&lt;210&gt; 98

&lt;211&gt; 4495

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 98

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&lt;210&gt; 99

&lt;211&gt; 1066

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 99

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      35          40          45
Gly Ser Leu Phe Gly Tyr Ser Val Ala Leu His Arg Gln Thr Glu Arg
      50          55          60
Gln Gln Arg Tyr Leu Leu Leu Ala Gly Ala Pro Arg Glu Leu Ala Val
      65          70          75          80
Pro Asp Gly Tyr Thr Asn Arg Thr Gly Ala Val Tyr Leu Cys Pro Leu
      85          90          95
Thr Ala His Lys Asp Asp Cys Glu Arg Met Asn Ile Thr Val Lys Asn
      100          105          110
Asp Pro Gly His His Ile Ile Glu Asp Met Trp Leu Gly Val Thr Val
      115          120          125
Ala Ser Gln Gly Pro Ala Gly Arg Val Leu Val Cys Ala His Arg Tyr
      130          135          140
Thr Gln Val Leu Trp Ser Gly Ser Glu Asp Gln Arg Arg Met Val Gly
      145          150          155          160
Lys Cys Tyr Val Arg Gly Asn Asp Leu Glu Leu Asp Ser Ser Asp Asp
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Trp Gln Thr Tyr His Asn Glu Met Cys Asn Ser Asn Thr Asp Tyr Leu
      180          185          190
Glu Thr Gly Met Cys Gln Leu Gly Thr Ser Gly Gly Phe Thr Gln Asn
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Thr Val Tyr Phe Gly Ala Pro Gly Ala Tyr Asn Trp Lys Gly Asn Ser
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Tyr Met Ile Gln Arg Lys Glu Trp Asp Leu Ser Glu Tyr Ser Tyr Lys
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Gln	Asp	Ile	Ala	Val	Gly	Ala	Pro	Phe	Glu	Gly	Leu	Gly	Lys	Val	Tyr
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Ser	Leu	Ser	Gly	Gln	Met	Asp	Val	Asp	Glu	Asn	Phe	Tyr	Pro	Asp	Leu
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Val	Ile	Asn	Ile	Val	His	Lys	Thr	Leu	Val	Pro	Arg	Pro	Ala	Val	Leu
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Thr	Leu	Ala	Tyr	Thr	Leu	Glu	Ala	Asp	Arg	Asp	Arg	Arg	Pro	Pro	Arg
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Leu	Arg	Phe	Ala	Gly	Ser	Glu	Ser	Ala	Val	Phe	His	Gly	Phe	Phe	Ser
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Leu	Arg	Asp	Lys	Leu	Arg	Pro	Ile	Ile	Ile	Ser	Met	Asn	Tyr	Ser	Leu
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Pro	Leu	Arg	Met	Pro	Asp	Arg	Pro	Arg	Leu	Gly	Leu	Arg	Ser	Leu	Asp
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Ala	Tyr	Pro	Ile	Leu	Asn	Gln	Ala	Gln	Ala	Leu	Glu	Asn	His	Thr	Glu
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<211> 4647
<212> DNA
<213> Homo sapiens
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&lt;210&gt; 101

&lt;211&gt; 788

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 101

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Glu Asp Tyr Pro Val Asp Leu Tyr Tyr Leu Met Asp Leu Ser Ala Ser
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Lys Glu Met Ser Lys Leu Thr Ser Asn Phe Arg Leu Gly Phe Gly Ser
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 <212> DNA  
 <213> Homo sapiens

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 Pro Pro Thr Ile His Tyr Pro Pro Ser Gln Gly Gln Met Asp Leu Cys  
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 180 185 190  
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 Thr Ser Glu Arg Lys Lys Glu Ile Tyr Glu Leu Ala Arg Lys Tyr Asp  
 210 215 220  
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&lt;210&gt; 105

&lt;211&gt; 408

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 105

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&lt;210&gt; 106

&lt;211&gt; 3103

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 106

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<210> 107  
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 <212> PRT  
 <213> Homo sapiens

<400> 107  
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&lt;210&gt; 108

&lt;211&gt; 2620

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 108

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&lt;210&gt; 109

&lt;211&gt; 401

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 109

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&lt;211&gt; 3944

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 110

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<212> PRT

<213> Homo sapiens

<400> 111

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Ser	Ser	Asp	Glu	Val	Cys	Asp	Gly	Asp	Arg	Glu	Lys	Glu	Glu	Pro	Pro	35	40	45	
Ser	Pro	Ile	Glu	Ala	Thr	Pro	Gln	Ser	Leu	Leu	Glu	Lys	Val	Ser		50	55	60	
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Pro	Lys	Pro	Pro	Lys	Pro	Pro	Lys	Pro	Pro	Arg	Pro	Pro	Lys	Thr	Leu	85	90	95	
Lys	Leu	Lys	Asp	Gly	Gly	Lys	Lys	Lys	Gly	Lys	Lys	Ser	Arg	Glu	Ser	100	105	110	
Ala	Ser	Pro	Thr	Ile	Pro	Asn	Leu	Asp	Leu	Leu	Glu	Ala	His	Thr	Lys	115	120	125	
Glu	Ala	Leu	Thr	Lys	Met	Glu	Pro	Pro	Lys	Lys	Gly	Lys	Ala	Thr	Lys	130	135	140	
Ser	Val	Leu	Ser	Val	Pro	Asn	Lys	Asp	Val	Val	His	Met	Gln	Asn	Asp	145	150	155	160
Val	Glu	Arg	Leu	Glu	Ile	Arg	Glu	Gln	Thr	Lys	Ser	Lys	Ser	Glu	Ala	165	170	175	
Lys	Trp	Lys	Tyr	Lys	Asn	Ser	Lys	Pro	Asp	Ser	Leu	Leu	Lys	Met	Glu	180	185	190	
Glu	Glu	Gln	Lys	Leu	Glu	Lys	Ser	Pro	Leu	Ala	Gly	Asn	Lys	Asp	Asn	195	200	205	
Lys	Phe	Ser	Phe	Ser	Phe	Ser	Asn	Lys	Lys	Leu	Leu	Gly	Ser	Lys	Ala	210	215	220	
Leu	Arg	Pro	Pro	Thr	Ser	Pro	Gly	Val	Phe	Gly	Ala	Leu	Gln	Asn	Phe	225	230	235	240
Lys	Glu	Asp	Lys	Pro	Lys	Pro	Val	Arg	Asp	Glu	Tyr	Glu	Tyr	Val	Ser	245	250	255	
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Leu	Pro	Thr	Pro	Val	Thr	Lys	Pro	Lys	Leu	Asp	Ser	Ala	Ala	Tyr	Lys	290	295	300	
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Thr	Lys	Pro	Gly	Arg	Asn	Ala	Arg	Val	Lys	Lys	Glu	Ser	Gly	Ser	Ser	325	330	335	
Ala	Ala	Gly	Ile	Leu	Asp	Leu	Leu	Gln	Ala	Ser	Glu	Glu	Val	Gly	Ala	340	345	350	
Leu	Glu	Tyr	Asn	Pro	Ser	Ser	Gln	Pro	Pro	Ala	Ser	Pro	Ser	Thr	Gln	355	360	365	
Glu	Ala	Ile	Gln	Gly	Met	Leu	Ser	Met	Ala	Asn	Leu	Gln	Ala	Ser	Asp	370	375	380	
Ser	Cys	Leu	Gln	Thr	Thr	Trp	Gly	Ala	Gly	Gln	Ala	Lys	Gly	Ser	Ser	385	390	395	400



Leu Ala Ala His Gly Ala Arg Lys Asn Gly Gly Gly Ser Gly Lys Ser  
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 Asp Asp Tyr Glu Glu Glu Gln Asp His Leu Asp Ala Cys Phe Lys Asp  
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 Ser Asp Tyr Val Tyr Pro Ser Leu Glu Ser Asp Glu Asp Asn Pro Ile  
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&lt;210&gt; 113

&lt;211&gt; 1713

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 113

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Ser Gln Leu Gln Ala Ser Tyr Val Glu Phe Arg Pro Ser Gln Gly Cys
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Ser Pro Gly Tyr Tyr Arg Asp His Lys Gly Leu Tyr Thr Gly Arg Cys
 50          55          60
Val Pro Cys Asn Cys Asn Gly His Ser Asn Gln Cys Gln Asp Gly Ser
 65          70          75          80
Gly Ile Cys Val Asn Cys Gln His Asn Thr Ala Gly Glu His Cys Glu
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Arg Cys Gln Glu Gly Tyr Tyr Gly Asn Ala Val His Gly Ser Cys Arg
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Gln Cys Glu Arg Cys Ala Pro Gly Tyr Phe Gly Asn Pro Gln Lys Phe
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165          170          175
Ser Cys His Pro Leu Thr Gly Asp Cys Ile Asn Gln Glu Pro Lys Asp
180          185          190
Ser Ser Pro Ala Glu Glu Cys Asp Asp Cys Asp Ser Cys Val Met Thr
195          200          205
Leu Leu Asn Asp Leu Ala Thr Met Gly Glu Gln Leu Arg Leu Val Lys
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Ser Gln Leu Gln Gly Leu Ser Ala Ser Ala Gly Leu Leu Glu Gln Met
225          230          235          240
Arg His Met Glu Thr Gln Ala Lys Asp Leu Arg Asn Gln Leu Leu Asn
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Tyr Arg Ser Ala Ile Ser Asn His Gly Ser Lys Ile Glu Gly Leu Glu
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Arg Glu Leu Thr Asp Leu Asn Gln Glu Phe Glu Thr Leu Gln Glu Lys

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Ile Arg Asn Val His Ile Leu Leu Lys	Gln Ile Ser Gly Thr Asp Gly	320
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Arg Lys Ala Asn Asp Ile Thr Asp Glu	Val Leu Asp Gly Leu Asn Pro	
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Ile Gln Thr Asp Val Glu Arg Ile Lys	Asp Thr Tyr Gly Arg Thr Gln	
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705	710	715
Lys Leu Thr Asn Lys Leu Pro Asp Leu	Trp Arg Lys Ile Glu Ser Ile	
725	730	735
Asn Gln Gln Leu Leu Pro Leu Gly Asn	Ile Ser Asp Asn Met Asp Arg	
740	745	750

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 Asp Lys Glu Ile Val Gly Thr Leu Leu Gly Phe Asp Asp Phe Val Asn  
                             35                            40                            45  
 Met Val Leu Glu Asp Val Thr Glu Phe Glu Ile Thr Pro Glu Gly Arg  
                             50                            55                            60  
 Arg Ile Thr Lys Leu Asp Gln Ile Leu Leu Asn Gly Asn Asn Ile Thr  
                             65                            70                            75                            80  
 Met Leu Val Pro Gly Gly Glu Gly Pro Glu Val

85

90

<210> 118  
 <211> 1717  
 <212> DNA  
 <213> Homo sapiens

<400> 118  
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 attggtggta ccagtggccg gtactatgat tatgatcttc ccctatcaat ttatgggcaa 180  
 tcatcaccaa actgtgcacc agaattgtaac tgccctgaaa gctacccaag tgccatgtac 240  
 tgtgatgagc tgaaattgaa aagtgtacca atgggtgcctc ctggaatcaa gtatctttac 300  
 cttaggaata accagattga ccatattgat gaaaaggcct ttgagaatgt aactgatctg 360  
 cagtggtctca ttctagatca caaccttcta gaaaactcca agataaaagg gagagttttc 420  
 tctaaattga aacaactgaa gaagctgcat ataaaccaca acaacctgac agagtctgtg 480  
 ggcccacttc ccaaactctc ggaggatctg cagcttactc ataacaagat cacaagctg 540  
 ggctcttttg aaggattggt aaacctgacc ttcatccatc tccagcacia tgggtgaaa 600  
 gaggatgctg tttcagctgc ttttaaaggc cttaaatcac tccaatacct tgacttgagc 660  
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 gtgtcatccc tgggtgagct ggatctgtcc tataacaagc ttaaaaaacat accaactgtc 900  
 aatgaaaacc ttgaaaacta ttacctggag gtcaatcaac ttgagaagtt tgacataaag 960  
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 aacgaagtca ctcttaatta atatctgtat cctggaacaa tattttatgg ttatgttttt 1140  
 ctgtgtgtca gttttcatag tatccatatt ttattactgt ttattacttc catgaatttt 1200  
 aaaatctgag ggaaatgttt tgtaaacatt tatttttttt aaagaaaaga tgaaaggcag 1260  
 gcctatttca tcacaagaac acacacatat acacgaatag acatcaaact caatgcttta 1320  
 tttgtaaatt tagtggtttt ttatttctac tgtcaaatga tgtgcaaaac cttttactgg 1380  
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 tggtaaaaaa atagggtgga gatattgagg ccaagaatat tgcaaaatat atgaagcttc 1560  
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 taataagcta ctagcaaaat aaaacatagc aaatggc 1717

<210> 119  
 <211> 338  
 <212> PRT  
 <213> Homo sapiens

<400> 119  
 Met Ser Leu Ser Ala Phe Thr Leu Phe Leu Ala Leu Ile Gly Gly Thr  
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 20 25 30  
 Ser Ser Pro Asn Cys Ala Pro Glu Cys Asn Cys Pro Glu Ser Tyr Pro  
 35 40 45  
 Ser Ala Met Tyr Cys Asp Glu Leu Lys Leu Lys Ser Val Pro Met Val  
 50 55 60  
 Pro Pro Gly Ile Lys Tyr Leu Tyr Leu Arg Asn Gln Ile Asp His  
 65 70 75 80  
 Ile Asp Glu Lys Ala Phe Glu Asn Val Thr Asp Leu Gln Trp Leu Ile  
 85 90 95  
 Leu Asp His Asn Leu Leu Glu Asn Ser Lys Ile Lys Gly Arg Val Phe  
 100 105 110

Ser Lys Leu Lys Gln Leu Lys Lys Leu His Ile Asn His Asn Asn Leu  
 115 120 125  
 Thr Glu Ser Val Gly Pro Leu Pro Lys Ser Leu Glu Asp Leu Gln Leu  
 130 135 140  
 Thr His Asn Lys Ile Thr Lys Leu Gly Ser Phe Glu Gly Leu Val Asn  
 145 150 155 160  
 Leu Thr Phe Ile His Leu Gln His Asn Arg Leu Lys Glu Asp Ala Val  
 165 170 175  
 Ser Ala Ala Phe Lys Gly Leu Lys Ser Leu Glu Tyr Leu Asp Leu Ser  
 180 185 190  
 Phe Asn Gln Ile Ala Arg Leu Pro Ser Gly Leu Pro Val Ser Leu Leu  
 195 200 205  
 Thr Leu Tyr Leu Asp Asn Asn Lys Ile Ser Asn Ile Pro Asp Glu Tyr  
 210 215 220  
 Phe Lys Arg Phe Asn Ala Leu Gln Tyr Leu Arg Leu Ser His Asn Glu  
 225 230 235 240  
 Leu Ala Asp Ser Gly Ile Pro Gly Asn Ser Phe Asn Val Ser Ser Leu  
 245 250 255  
 Val Glu Leu Asp Leu Ser Tyr Asn Lys Leu Lys Asn Ile Pro Thr Val  
 260 265 270  
 Asn Glu Asn Leu Glu Asn Tyr Tyr Leu Glu Val Asn Gln Leu Glu Lys  
 275 280 285  
 Phe Asp Ile Lys Ser Phe Cys Lys Ile Leu Gly Pro Leu Ser Tyr Ser  
 290 295 300  
 Lys Ile Lys His Leu Arg Leu Asp Gly Asn Arg Ile Ser Glu Thr Ser  
 305 310 315 320  
 Leu Pro Pro Asp Met Tyr Glu Cys Leu Arg Val Ala Asn Glu Val Thr  
 325 330 335  
 Leu Asn

&lt;210&gt; 120

&lt;211&gt; 1334

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 120

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 caatggagac ttatccccc aagggtgaagg ggagtcgccc cctgtgaacg gaacagatga 180  
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 gcctttcaaa ttgagcggcc tgtccttcaa gagaaatcgg aaggagggtg ggggtgattc 360  
 ttctgcctcc tcaccacacag aggaagagca ggagcagggg gagatcgggt cctgcagcga 420  
 cgagggcact gctcaggaag ggaaggccgc agccaccctc gagagccagg aaccccaggc 480  
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 atccactccc tcggggccgg agagtggccc tacaccagcc agcgctgagc agaatgagta 600  
 gctaggtagg ggcaggtggg tgatctctaa gctgcaaaaa ctgtgctgtc cttgtgaggt 660  
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 ctccctcccag ccacgttccc ttctctctc tccctcctgt ggattctccc atcagccatc 780  
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 cagttgttgg ttttcttccc caattctttt ccaagtaggt tttgtttacc ctactcccca 960  
 aatccctgag ccagaagtgg ggtgcttata tccccaaacc ttgagtgtcc agccttcccc 1020  
 tgttgttttt agtctcttgt gctgtgccta gtggcacctg ggctggggag gacactgccc 1080  
 cgtctaggtt tttataaatg tcttactcaa gttcaaacct ccagcctgtg aatcaactgt 1140  
 gtctcttttt tgacttggtg agcaagtatt aggccttggg gtggggggag gtctgtaatg 1200  
 tgaacaact tcttgtcttt ttttctccca ctgttgtaaa taacttttaa tggccaaacc 1260

ccagatttgt actttttttt tttttctaac tgctaaaacc attctcttcc acctggtttt 1320  
actgtaacat ttgg 1334

<210> 121  
<211> 195  
<212> PRT  
<213> Homo sapiens

<400> 121  
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Glu Ala Ala Gly Ala Ser Pro Ala Lys Ala Asn Gly Gln Glu Asn Gly  
20 25 30  
His Val Lys Ser Asn Gly Asp Leu Ser Pro Lys Gly Glu Gly Glu Ser  
35 40 45  
Pro Pro Val Asn Gly Thr Asp Glu Ala Ala Gly Ala Thr Gly Asp Ala  
50 55 60  
Ile Glu Pro Ala Pro Pro Ser Gln Gly Ala Glu Ala Lys Gly Glu Val  
65 70 75 80  
Pro Pro Lys Glu Thr Pro Lys Lys Lys Lys Lys Phe Ser Phe Lys Lys  
85 90 95  
Pro Phe Lys Leu Ser Gly Leu Ser Phe Lys Arg Asn Arg Lys Glu Gly  
100 105 110  
Gly Gly Asp Ser Ser Ala Ser Ser Pro Thr Glu Glu Glu Gln Glu Gln  
115 120 125  
Gly Glu Ile Gly Ala Cys Ser Asp Glu Gly Thr Ala Gln Glu Gly Lys  
130 135 140  
Ala Ala Ala Thr Pro Glu Ser Gln Glu Pro Gln Ala Lys Gly Ala Glu  
145 150 155 160  
Ala Ser Ala Ala Ser Glu Glu Glu Ala Gly Pro Gln Ala Thr Glu Pro  
165 170 175  
Ser Thr Pro Ser Gly Pro Glu Ser Gly Pro Thr Pro Ala Ser Ala Glu  
180 185 190  
Gln Asn Glu  
195

<210> 122  
<211> 1081  
<212> DNA  
<213> Homo sapiens

<400> 122  
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gctgcctacc tcttctgtct attcctgcct gcaggcttgc tggtcaggg ccagtatgat 180  
ctggaccgcg tgccgccgtt ccctgaccac gtccagtaca ccactatag cgaccagatc 240  
gacaaccag actactatga ttatcaagag gtgactcctc ggccctccga ggaacagttc 300  
cagttccagt ccagcagca agtccaacag gaagtcaccc cagccccaac ccagaacca 360  
ggaaatgcag agctggagcc cacagagcct gggcctcttg actgccgtga ggaacagtac 420  
ccgtgcaccc gcctctactc catacacagg ccttgcaaac agtgtctcaa cgaggtctgc 480  
ttctacagcc tccgccgtgt gtacgtcatt aacaaggaga tctgtgttcg tacagtgtgt 540  
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acagtcccc gaggtaggct acatcccccc accccagctg gtctgcttgg atttcctaca 1020  
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 a 1081

<210> 123  
 <211> 183  
 <212> PRT  
 <213> Homo sapiens

<400> 123  
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 Ala Gln Gly Gln Tyr Asp Leu Asp Pro Leu Pro Pro Phe Pro Asp His  
 20 25 30  
 Val Gln Tyr Thr His Tyr Ser Asp Gln Ile Asp Asn Pro Asp Tyr Tyr  
 35 40 45  
 Asp Tyr Gln Glu Val Thr Pro Arg Pro Ser Glu Glu Gln Phe Gln Phe  
 50 55 60  
 Gln Ser Gln Gln Gln Val Gln Gln Glu Val Ile Pro Ala Pro Thr Pro  
 65 70 75 80  
 Glu Pro Gly Asn Ala Glu Leu Glu Pro Thr Glu Pro Gly Pro Leu Asp  
 85 90 95  
 Cys Arg Glu Glu Gln Tyr Pro Cys Thr Arg Leu Tyr Ser Ile His Arg  
 100 105 110  
 Pro Cys Lys Gln Cys Leu Asn Glu Val Cys Phe Tyr Ser Leu Arg Arg  
 115 120 125  
 Val Tyr Val Ile Asn Lys Glu Ile Cys Val Arg Thr Val Cys Ala His  
 130 135 140  
 Glu Glu Leu Leu Arg Ala Asp Leu Cys Arg Asp Lys Phe Ser Lys Cys  
 145 150 155 160  
 Gly Val Met Ala Ser Ser Gly Leu Cys Gln Ser Val Ala Ala Ser Cys  
 165 170 175  
 Ala Arg Ser Cys Gly Ser Cys  
 180

<210> 124  
 <211> 1066  
 <212> DNA  
 <213> Homo sapiens

<400> 124  
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 ctgctattcc tgctgcagg cttgctggct cagggccagt atgatctgga cccgctgccg 180  
 ccgttccttg accacgtcca gtacacccac tatagcgacc agatcgacaa ccagactac 240  
 tatgattatc aagaggtgac tcctcggccc tccgaggaac agttccagtt ccagtcccag 300  
 cagcaagtcc aacaggaagt catcccagcc ccaaccccag aaccaggaaa tgcagagctg 360  
 gagccacag agcctgggcc tcttgactgc cgtgaggaac agtaccctg caccgcctc 420  
 tactccatac acaggccttg caaacagtg tccaacgagg tctgcttcta cagcctccgc 480  
 cgtgtgtacg tcattaacaa ggagatctgt gttcgtacag tgtgtgccc cgaggagctc 540  
 ctccgagctg acctctgtcg ggacaagttc tccaaatgtg gcgtgatggc cagcagcggc 600  
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 ggcacacctga gtctggccc tcctgggata tggggccctc gggctacctg acctggtgct 720  
 tttttcccca tcccatgtt ccttttattc tgaaaaagtt agtggactgc agccctgggg 780  
 gttgcaggct gcgtgcctc aggcctctc ttcagcctgt ggccacctc ggggcacgat 840  
 gggggctccc cactgccag tctgcccctc ggggtgggg agtatccag gcctctctgt 900  
 gggacctggg cctgacgggc ccttctcagc ccgttttgag gacagacagt ccccgaggt 960  
 aggctacatc ccccaacccc agctgggtctg cttggatttc ctacagcccc cgtgggcatg 1020

gaccaccttt attttataca aaattaaaaa caagttttta caaaaa

1066

&lt;210&gt; 125

&lt;211&gt; 183

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 125

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Met Arg Ala Ala Tyr Leu Phe Leu Leu Phe Leu Pro Ala Gly Leu Leu
 1           5           10           15
Ala Gln Gly Gln Tyr Asp Leu Asp Pro Leu Pro Pro Phe Pro Asp His
          20           25           30
Val Gln Tyr Thr His Tyr Ser Asp Gln Ile Asp Asn Pro Asp Tyr Tyr
          35           40           45
Asp Tyr Gln Glu Val Thr Pro Arg Pro Ser Glu Glu Gln Phe Gln Phe
 50           55           60
Gln Ser Gln Gln Gln Val Gln Gln Glu Val Ile Pro Ala Pro Thr Pro
 65           70           75           80
Glu Pro Gly Asn Ala Glu Leu Glu Pro Thr Glu Pro Gly Pro Leu Asp
          85           90           95
Cys Arg Glu Glu Gln Tyr Pro Cys Thr Arg Leu Tyr Ser Ile His Arg
          100          105          110
Pro Cys Lys Gln Cys Leu Asn Glu Val Cys Phe Tyr Ser Leu Arg Arg
          115          120          125
Val Tyr Val Ile Asn Lys Glu Ile Cys Val Arg Thr Val Cys Ala His
          130          135          140
Glu Glu Leu Leu Arg Ala Asp Leu Cys Arg Asp Lys Phe Ser Lys Cys
145          150          155          160
Gly Val Met Ala Ser Ser Gly Leu Cys Gln Ser Val Ala Ala Ser Cys
          165          170          175
Ala Arg Ser Cys Gly Ser Cys
          180

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&lt;210&gt; 126

&lt;211&gt; 1611

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 126

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gatcatggtc tggatctgca acacggggcca ggccaaagtc acagatcttg agatcacagg 120
tgggtgttgag cagcaggcag gcaggcaatc ggcccgagtg gctgtcggct cttcagctct 180
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cattatcttg accagctgaa tcacattttg ggtattcttg gatccccatc acaagaagac 1080
ctgaattgta taataaattt aaaagctagg aactatttgc tttctcttcc acacaaaaat 1140

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aaggtgccat ggaacaggct gttcccaaat gctgactcca aagctctgga cttattggac 1200
aaaatgttga cattcaaccc acacaagagg attgaagtag aacaggctct ggcccaccca 1260
tatctggagc agtattacga cccgagtgac gagcccatcg ccgaagcacc attcaagttc 1320
gacatggaat tggatgactt gcctaaggaa aagctaaaag aactaatttt tgaagagact 1380
gctagattcc agccaggata cagatcttaa atttgtcagg acaagggctc agaggactgg 1440
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cgtcttggct tatccacttt gactcctttg agccgtttgg aggggcgggt tctggtagtt 1560
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<210> 127  
 <211> 360  
 <212> PRT  
 <213> Homo sapiens

<400> 127

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Gln	Val	Phe	Asp	Val	Gly	Pro	Arg	Tyr	Thr	Asn	Leu	Ser	Tyr	Ile	Gly	20	25	30	35
Glu	Gly	Ala	Tyr	Gly	Met	Val	Cys	Ser	Ala	Tyr	Asp	Asn	Val	Asn	Lys	40	45	50	55
Val	Arg	Val	Ala	Ile	Lys	Lys	Ile	Ser	Pro	Phe	Glu	His	Gln	Thr	Tyr	60	65	70	75
Cys	Gln	Arg	Thr	Leu	Arg	Glu	Ile	Lys	Ile	Leu	Leu	Arg	Phe	Arg	His	80	85	90	95
Glu	Asn	Ile	Ile	Gly	Ile	Asn	Asp	Ile	Ile	Arg	Ala	Pro	Thr	Ile	Glu	100	105	110	115
Gln	Met	Lys	Asp	Val	Tyr	Ile	Val	Gln	Asp	Leu	Met	Glu	Thr	Asp	Leu	120	125	130	135
Tyr	Lys	Leu	Leu	Lys	Thr	Gln	His	Leu	Ser	Asn	Asp	His	Ile	Cys	Tyr	140	145	150	155
Phe	Leu	Tyr	Gln	Ile	Leu	Arg	Gly	Leu	Lys	Tyr	Ile	His	Ser	Ala	Asn	160	165	170	175
Val	Leu	His	Arg	Asp	Leu	Lys	Pro	Ser	Asn	Leu	Leu	Leu	Asn	Thr	Thr	180	185	190	195
Cys	Asp	Leu	Lys	Ile	Cys	Asp	Phe	Gly	Leu	Ala	Arg	Val	Ala	Asp	Pro	200	205	210	215
Asp	His	Asp	His	Thr	Gly	Phe	Leu	Thr	Glu	Tyr	Val	Ala	Thr	Arg	Trp	220	225	230	235
Tyr	Arg	Ala	Pro	Glu	Ile	Met	Leu	Asn	Ser	Lys	Gly	Tyr	Thr	Lys	Ser	240	245	250	255
Ile	Asp	Ile	Trp	Ser	Val	Gly	Cys	Ile	Leu	Ala	Glu	Met	Leu	Ser	Asn	260	265	270	275
Arg	Pro	Ile	Phe	Pro	Gly	Lys	His	Tyr	Leu	Asp	Gln	Leu	Asn	His	Ile	280	285	290	295
Leu	Gly	Ile	Leu	Gly	Ser	Pro	Ser	Gln	Glu	Asp	Leu	Asn	Cys	Ile	Ile	300	305	310	315
Asn	Leu	Lys	Ala	Arg	Asn	Tyr	Leu	Leu	Ser	Leu	Pro	His	Lys	Asn	Lys	320	325	330	335
Val	Pro	Trp	Asn	Arg	Leu	Phe	Pro	Asn	Ala	Asp	Ser	Lys	Ala	Leu	Asp	340	345	350	355
Leu	Leu	Asp	Lys	Met	Leu	Thr	Phe	Asn	Pro	His	Lys	Arg	Ile	Glu	Val	360	365	370	375
Glu	Gln	Ala	Leu	Ala	His	Pro	Tyr	Leu	Glu	Gln	Tyr	Tyr	Asp	Pro	Ser	380	385	390	395
Asp	Glu	Pro	Ile	Ala	Glu	Ala	Pro	Phe	Lys	Phe	Asp	Met	Glu	Leu	Asp	400	405	410	415
Asp	Leu	Pro	Lys	Glu	Lys	Leu	Lys	Glu	Leu	Ile	Phe	Glu	Glu	Thr	Ala	420	425	430	435

Arg Phe Gln Pro Gly Tyr Arg Ser  
355 360

<210> 128  
<211> 2917  
<212> DNA  
<213> Homo sapiens

<400> 128  
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cgaggtggcc gagaagtgcc agaaactggt cctggacttc ttggaggagt ttcagagcag 180  
cgatggagaa attaaatact tgcaattagc agaggaactg attcgctctg agagaaacac 240  
attggttgtg agttttgtgg acctggaaca atttaaccag caactttcca ccaccattca 300  
agaggagttc tatagagttt acccttacct gtgtcgggccc ttgaaaacat tcgtcaaaga 360  
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acacaagatt cgagagctca cctcatccag aattggtttg ctactcgcga tcagtgggca 480  
ggtggtgcgg actcaccagc ttcaccacaga gcttgtgagc ggaacttttc tgtgcttgga 540  
ctgtcagaca gtgatcaggg atgtagaaca gcagttcaaa tacacacagc caaacatctg 600  
ccgaaatcca gtttgtgcc aacaggaggag attcttactg gatacaaaata aatcaagatt 660  
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ccccgcagc ttagaagtaa ttttaagggc tgaagctgtg gaatcagctc aagctggtga 780  
caagtgtgac tttacagggg cactgattgt tgtgcctgac gtctccaagc ttagcacacc 840  
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<210> 129  
 <211> 821  
 <212> PRT  
 <213> Homo sapiens

<400> 129

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Phe	Leu	Glu	Glu	Phe	Gln	Ser	Ser	Asp	Gly	Glu	Ile	Lys	Tyr	Leu	Gln
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Phe	Val	Asp	Leu	Glu	Gln	Phe	Asn	Gln	Gln	Leu	Ser	Thr	Thr	Ile	Gln
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Glu	Glu	Phe	Tyr	Arg	Val	Tyr	Pro	Tyr	Leu	Cys	Arg	Ala	Leu	Lys	Thr
				85					90					95	
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Ala	Phe	Gln	Asp	Leu	Pro	Thr	Arg	His	Lys	Ile	Arg	Glu	Leu	Thr	Ser
		115					120					125			
Ser	Arg	Ile	Gly	Leu	Leu	Thr	Arg	Ile	Ser	Gly	Gln	Val	Val	Arg	Thr
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His	Pro	Val	His	Pro	Glu	Leu	Val	Ser	Gly	Thr	Phe	Leu	Cys	Leu	Asp
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Cys	Gln	Thr	Val	Ile	Arg	Asp	Val	Glu	Gln	Gln	Phe	Lys	Tyr	Thr	Gln
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Pro	Asn	Ile	Cys	Arg	Asn	Pro	Val	Cys	Ala	Asn	Arg	Arg	Arg	Phe	Leu
			180					185					190		
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Gln	Glu	Thr	Gln	Ala	Glu	Leu	Pro	Arg	Gly	Ser	Ile	Pro	Arg	Ser	Leu
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Glu	Val	Ile	Leu	Arg	Ala	Glu	Ala	Val	Glu	Ser	Ala	Gln	Ala	Gly	Asp
225					230					235					240
Lys	Cys	Asp	Phe	Thr	Gly	Thr	Leu	Ile	Val	Val	Pro	Asp	Val	Ser	Lys
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Val	Asp	Gly	Tyr	Glu	Thr	Glu	Gly	Ile	Arg	Gly	Leu	Arg	Ala	Leu	Gly
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Val	Arg	Asp	Leu	Ser	Tyr	Arg	Leu	Val	Phe	Leu	Ala	Cys	Cys	Val	Ala
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Thr	Ala	Glu	Ser	Ile	Lys	Asn	Gln	Met	Thr	Val	Lys	Glu	Trp	Glu	Lys
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Val	Phe	Glu	Met	Ser	Gln	Asp	Lys	Asn	Leu	Tyr	His	Asn	Leu	Cys	Thr
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Ser	Leu	Phe	Pro	Thr	Ile	His	Gly	Asn	Asp	Glu	Val	Lys	Arg	Gly	Val
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Leu	Leu	Met	Leu	Phe	Gly	Gly	Val	Pro	Lys	Thr	Thr	Gly	Glu	Gly	Thr
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Ala	Lys	Ser	Gln	Phe	Leu	Lys	His	Val	Glu	Glu	Phe	Ser	Pro	Arg	Ala
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Val	Tyr	Thr	Ser	Gly	Lys	Ala	Ser	Ser	Ala	Ala	Gly	Leu	Thr	Ala	Ala		
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Thr	Ile	Ser	Ile	Thr	Lys	Ala	Gly	Val	Lys	Ala	Thr	Leu	Asn	Ala	Arg		
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Arg	Phe	Asp	Leu	Phe	Phe	Ile	Leu	Val	Asp	Glu	Cys	Asn	Glu	Val	Thr		
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Phe	Ile	Val	Glu	Gln	Tyr	Lys	His	Leu	Arg	Gln	Arg	Asp	Gly	Ser	Gly		
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Val	Thr	Lys	Ser	Ser	Trp	Arg	Ile	Thr	Val	Arg	Gln	Leu	Glu	Ser	Met		
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Gln	Pro	Lys	His	Val	Lys	Glu	Ala	Phe	Arg	Leu	Leu	Asn	Lys	Ser	Ile		
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Gln	Glu	Ser	Ala	Pro	Lys	Ala	Ser	Leu	Arg	Leu	Gly	Phe	Ser	Glu	Tyr		
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Cys	Arg	Ile	Ser	Asn	Leu	Ile	Val	Leu	His	Leu	Arg	Lys	Val	Glu	Glu		
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Glu	Glu	Asp	Glu	Ser	Ala	Leu	Lys	Arg	Ser	Glu	Leu	Val	Asn	Trp	Tyr		
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Leu	Lys	Glu	Ile	Glu	Ser	Glu	Ile	Asp	Ser	Glu	Glu	Glu	Leu	Ile	Asn		
		755					760							765			
Lys	Lys	Arg	Ile	Ile	Glu	Lys	Val	Ile	His	Arg	Leu	Thr	His	Tyr	Asp		
		770				775					780						
His	Val	Leu	Ile	Glu	Leu	Thr	Gln	Ala	Gly	Leu	Lys	Gly	Ser	Thr	Glu		
785					790					795					800		
Gly	Ser	Glu	Ser	Tyr	Glu	Glu	Asp	Pro	Tyr	Leu	Val	Val	Asn	Pro	Asn		
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&lt;210&gt; 130

&lt;211&gt; 786

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 130

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&lt;210&gt; 131

&lt;211&gt; 143

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 131

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Leu Thr Ser Ala Val Ala Lys Lys Lys Asp Lys Val Lys Lys Gly Gly
20          25          30
Pro Gly Ser Glu Cys Ala Glu Trp Ala Trp Gly Pro Cys Thr Pro Ser
35          40          45
Ser Lys Asp Cys Gly Val Gly Phe Arg Glu Gly Thr Cys Gly Ala Gln
50          55          60
Thr Gln Arg Ile Arg Cys Arg Val Pro Cys Asn Trp Lys Lys Glu Phe
65          70          75          80
Gly Ala Asp Cys Lys Tyr Lys Phe Glu Asn Trp Gly Ala Cys Asp Gly
85          90          95
Gly Thr Gly Thr Lys Val Arg Gln Gly Thr Leu Lys Lys Ala Arg Tyr
100         105         110
Asn Ala Gln Cys Gln Glu Thr Ile Arg Val Thr Lys Pro Cys Thr Pro
115         120         125
Lys Thr Lys Ala Lys Ala Lys Ala Lys Lys Gly Lys Gly Lys Asp
130         135         140

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&lt;210&gt; 132

&lt;211&gt; 603

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 132

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 <211> 103  
 <212> PRT  
 <213> Homo sapiens

<400> 133  
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 Pro Phe Ile Asn Arg Arg Asn Ala Asn Thr Phe Ile Ser Pro Gln Gln  
 35 40 45  
 Arg Trp Arg Ala Lys Val Gln Glu Arg Ile Arg Glu Arg Ser Lys Pro  
 50 55 60  
 Val His Glu Leu Asn Arg Glu Ala Cys Asp Asp Tyr Arg Leu Cys Glu  
 65 70 75 80  
 Arg Tyr Ala Met Val Tyr Gly Tyr Asn Ala Ala Tyr Asn Arg Tyr Phe  
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 Arg Lys Arg Arg Gly Ala Lys  
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 <211> 1778  
 <212> DNA  
 <213> Homo sapiens

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 <211> 470  
 <212> PRT  
 <213> Homo sapiens

<400> 135

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			20					25					30		
Gly	Glu	Arg	Tyr	Leu	Glu	Lys	Phe	Tyr	Gly	Leu	Glu	Ile	Asn	Lys	Leu
		35					40					45			
Pro	Val	Thr	Lys	Met	Lys	Tyr	Ser	Gly	Asn	Leu	Met	Lys	Glu	Lys	Ile
	50				55						60				
Gln	Glu	Met	Gln	His	Phe	Leu	Gly	Leu	Lys	Val	Thr	Gly	Gln	Leu	Asp
65				70						75				80	
Thr	Ser	Thr	Leu	Glu	Met	Met	His	Ala	Pro	Arg	Cys	Gly	Val	Pro	Asp
			85					90						95	
Leu	His	His	Phe	Arg	Glu	Met	Pro	Gly	Gly	Pro	Val	Trp	Arg	Lys	His
			100					105					110		
Tyr	Ile	Thr	Tyr	Arg	Ile	Asn	Asn	Tyr	Thr	Pro	Asp	Met	Asn	Arg	Glu
		115					120					125			
Asp	Val	Asp	Tyr	Ala	Ile	Arg	Lys	Ala	Phe	Gln	Val	Trp	Ser	Asn	Val
	130					135					140				
Thr	Pro	Leu	Lys	Phe	Ser	Lys	Ile	Asn	Thr	Gly	Met	Ala	Asp	Ile	Leu
145					150					155					160
Val	Val	Phe	Ala	Arg	Gly	Ala	His	Gly	Asp	Phe	His	Ala	Phe	Asp	Gly
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Lys	Gly	Gly	Ile	Leu	Ala	His	Ala	Phe	Gly	Pro	Gly	Ser	Gly	Ile	Gly
			180					185					190		
Gly	Asp	Ala	His	Phe	Asp	Glu	Asp	Glu	Phe	Trp	Thr	Thr	His	Ser	Gly
	195					200						205			
Gly	Thr	Asn	Leu	Phe	Leu	Thr	Ala	Val	His	Glu	Ile	Gly	His	Ser	Leu
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Gly	Leu	Gly	His	Ser	Ser	Asp	Pro	Lys	Ala	Val	Met	Phe	Pro	Thr	Tyr
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Lys	Tyr	Val	Asp	Ile	Asn	Thr	Phe	Arg	Leu	Ser	Ala	Asp	Asp	Ile	Arg
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Asp	Ala	Val	Thr	Thr	Val	Gly	Asn	Lys	Ile	Phe	Phe	Phe	Lys	Asp	Arg
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Phe	Phe	Trp	Leu	Lys	Val	Ser	Glu	Arg	Pro	Lys	Thr	Ser	Val	Asn	Leu
305					310					315					320
Ile	Ser	Ser	Leu	Trp	Pro	Thr	Leu	Pro	Ser	Gly	Ile	Glu	Ala	Ala	Tyr
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Glu	Ile	Glu	Ala	Arg	Asn	Gln	Val	Phe	Leu	Phe	Lys	Asp	Asp	Lys	Tyr
		340						345					350		
Trp	Leu	Ile	Ser	Asn	Leu	Arg	Pro	Glu	Pro	Asn	Tyr	Pro	Lys	Ser	Ile
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His	Ser	Phe	Gly	Phe	Pro	Asn	Phe	Val	Lys	Lys	Ile	Asp	Ala	Ala	Val
	370					375					380				
Phe	Asn	Pro	Arg	Phe	Tyr	Arg	Thr	Tyr	Phe	Phe	Val	Asp	Asn	Gln	Tyr
385					390					395					400
Trp	Arg	Tyr	Asp	Glu	Arg	Arg	Gln	Met	Met	Asp	Pro	Gly	Tyr	Pro	Lys
			405						410					415	

Leu Ile Thr Lys Asn Phe Gln Gly Ile Gly Pro Lys Ile Asp Ala Val  
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 Phe Tyr Ser Lys Asn Lys Tyr Tyr Tyr Phe Phe Gln Gly Ser Asn Gln  
                   435                                  440                  445  
 Phe Glu Tyr Asp Phe Leu Leu Gln Arg Ile Thr Lys Thr Leu Lys Ser  
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 Asn Ser Trp Phe Gly Cys  
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 <212> DNA  
 <213> Homo sapiens

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<210> 137  
 <211> 477  
 <212> PRT  
 <213> Homo sapiens

<400> 137  
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                   20                                  25                  30  
 Leu Val Gln Lys Tyr Leu Glu Asn Tyr Tyr Asp Leu Lys Lys Asp Val



		35				40				45					
Lys	Gln	Phe	Val	Arg	Arg	Lys	Asp	Ser	Gly	Pro	Val	Val	Lys	Lys	Ile
	50					55					60				
Arg	Glu	Met	Gln	Lys	Phe	Leu	Gly	Leu	Glu	Val	Thr	Gly	Lys	Leu	Asp
65					70					75					80
Ser	Asp	Thr	Leu	Glu	Val	Met	Arg	Lys	Pro	Arg	Cys	Gly	Val	Pro	Asp
				85					90					95	
Val	Gly	His	Phe	Arg	Thr	Phe	Pro	Gly	Ile	Pro	Lys	Trp	Arg	Lys	Thr
			100					105					110		
His	Leu	Thr	Tyr	Arg	Ile	Val	Asn	Tyr	Thr	Pro	Asp	Leu	Pro	Lys	Asp
		115					120					125			
Ala	Val	Asp	Ser	Ala	Val	Glu	Lys	Ala	Leu	Lys	Val	Trp	Glu	Glu	Val
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Thr	Pro	Leu	Thr	Phe	Ser	Arg	Leu	Tyr	Glu	Gly	Glu	Ala	Asp	Ile	Met
145					150					155					160
Ile	Ser	Phe	Ala	Val	Arg	Glu	His	Gly	Asp	Phe	Tyr	Pro	Phe	Asp	Gly
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Pro	Gly	Asn	Val	Leu	Ala	His	Ala	Tyr	Ala	Pro	Gly	Pro	Gly	Ile	Asn
		180						185					190		
Gly	Asp	Ala	His	Phe	Asp	Asp	Asp	Glu	Gln	Trp	Thr	Lys	Asp	Thr	Thr
	195					200						205			
Gly	Thr	Asn	Leu	Phe	Leu	Val	Ala	Ala	His	Glu	Ile	Gly	His	Ser	Leu
	210					215					220				
Gly	Leu	Phe	His	Ser	Ala	Asn	Thr	Glu	Ala	Leu	Met	Tyr	Pro	Leu	Tyr
225					230					235					240
His	Ser	Leu	Thr	Asp	Leu	Thr	Arg	Phe	Arg	Leu	Ser	Gln	Asp	Asp	Ile
				245					250					255	
Asn	Gly	Ile	Gln	Ser	Leu	Tyr	Gly	Pro	Pro	Pro	Asp	Ser	Pro	Glu	Thr
			260					265					270		
Pro	Leu	Val	Pro	Thr	Glu	Pro	Val	Pro	Pro	Glu	Pro	Gly	Thr	Pro	Ala
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Asn	Cys	Asp	Pro	Ala	Leu	Ser	Phe	Asp	Ala	Val	Ser	Thr	Leu	Arg	Gly
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Glu	Ile	Leu	Ile	Phe	Lys	Asp	Arg	His	Phe	Trp	Arg	Lys	Ser	Leu	Arg
305					310					315					320
Lys	Leu	Glu	Pro	Glu	Leu	His	Leu	Ile	Ser	Ser	Phe	Trp	Pro	Ser	Leu
				325					330					335	
Pro	Ser	Gly	Val	Asp	Ala	Ala	Tyr	Glu	Val	Thr	Ser	Lys	Asp	Leu	Val
			340					345					350		
Phe	Ile	Phe	Lys	Gly	Asn	Gln	Phe	Trp	Ala	Ile	Arg	Gly	Asn	Glu	Val
	355						360					365			
Arg	Ala	Gly	Tyr	Pro	Arg	Gly	Ile	His	Thr	Leu	Gly	Phe	Pro	Pro	Thr
	370					375					380				
Val	Arg	Lys	Ile	Asp	Ala	Ala	Ile	Ser	Asp	Lys	Glu	Lys	Asn	Lys	Thr
385					390					395					400
Tyr	Phe	Phe	Val	Glu	Asp	Lys	Tyr	Trp	Arg	Phe	Asp	Glu	Lys	Arg	Asn
				405					410					415	
Ser	Met	Glu	Pro	Gly	Phe	Pro	Lys	Gln	Ile	Ala	Glu	Asp	Phe	Pro	Gly
			420					425					430		
Ile	Asp	Ser	Lys	Ile	Asp	Ala	Val	Phe	Glu	Glu	Phe	Gly	Phe	Phe	Tyr
	435						440					445			
Phe	Phe	Thr	Gly	Ser	Ser	Gln	Leu	Glu	Phe	Asp	Pro	Asn	Ala	Lys	Lys
	450					455					460				
Val	Thr	His	Thr	Leu	Lys	Ser	Asn	Ser	Trp	Leu	Asn	Cys			
465					470						475				

&lt;210&gt; 138

&lt;211&gt; 1127

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 138

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gaggcatgag tgagctacag tgggaacagg ctcaggacta tctcaagaga ttttatctct 180
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&lt;210&gt; 139

&lt;211&gt; 267

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 139

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20      25      30
Glu Gln Ala Gln Asp Tyr Leu Lys Arg Phe Tyr Leu Tyr Asp Ser Glu
35      40      45
Thr Lys Asn Ala Asn Ser Leu Glu Ala Lys Leu Lys Glu Met Gln Lys
50      55      60
Phe Phe Gly Leu Pro Ile Thr Gly Met Leu Asn Ser Arg Val Ile Glu
65      70      75      80
Ile Met Gln Lys Pro Arg Cys Gly Val Pro Asp Val Ala Glu Tyr Ser
85      90      95
Leu Phe Pro Asn Ser Pro Lys Trp Thr Ser Lys Val Val Thr Tyr Arg
100     105     110
Ile Val Ser Tyr Thr Arg Asp Leu Pro His Ile Thr Val Asp Arg Leu
115     120     125
Val Ser Lys Ala Leu Asn Met Trp Gly Lys Glu Ile Pro Leu His Phe
130     135     140
Arg Lys Val Val Trp Gly Thr Ala Asp Ile Met Ile Gly Phe Ala Arg
145     150     155     160
Gly Ala His Gly Asp Ser Tyr Pro Phe Asp Gly Pro Gly Asn Thr Leu
165     170     175
Ala His Ala Phe Ala Pro Gly Thr Gly Leu Gly Gly Asp Ala His Phe
180     185     190
Asp Glu Asp Glu Arg Trp Thr Asp Gly Ser Ser Leu Gly Ile Asn Phe
195     200     205
Leu Tyr Ala Ala Thr His Glu Leu Gly His Ser Leu Gly Met Gly His
210     215     220
Ser Ser Asp Pro Asn Ala Val Met Tyr Pro Thr Tyr Gly Asn Gly Asp

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225	230	235	240
Pro Gln Asn Phe Lys Leu Ser Gln Asp Asp Ile Lys Gly Ile Gln Lys			
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Leu Tyr Gly Lys Arg Ser Asn Ser Arg Lys Lys			
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<210> 140  
 <211> 1078  
 <212> DNA  
 <213> Homo sapiens

<400> 140

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<210> 141  
 <211> 2334  
 <212> DNA  
 <213> Homo sapiens

<400> 141

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&lt;210&gt; 142

&lt;211&gt; 707

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 142

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  20          25          30
Gly Asp Leu Arg Thr Asn Leu Thr Asp Arg Gln Leu Ala Glu Glu Tyr
  35          40          45
Leu Tyr Arg Tyr Gly Tyr Thr Arg Val Ala Glu Met Arg Gly Glu Ser
  50          55          60
Lys Ser Leu Gly Pro Ala Leu Leu Leu Leu Gln Lys Gln Leu Ser Leu
  65          70          75          80
Pro Glu Thr Gly Glu Leu Asp Ser Ala Thr Leu Lys Ala Met Arg Thr
  85          90          95
Pro Arg Cys Gly Val Pro Asp Leu Gly Arg Phe Gln Thr Phe Glu Gly
  100         105         110
Asp Leu Lys Trp His His His Asn Ile Thr Tyr Trp Ile Gln Asn Tyr
  115         120         125
Ser Glu Asp Leu Pro Arg Ala Val Ile Asp Asp Ala Phe Ala Arg Ala
  130         135         140
Phe Ala Leu Trp Ser Ala Val Thr Pro Leu Thr Phe Thr Arg Val Tyr
  145         150         155         160
Ser Arg Asp Ala Asp Ile Val Ile Gln Phe Gly Val Ala Glu His Gly
  165         170         175
Asp Gly Tyr Pro Phe Asp Gly Lys Asp Gly Leu Leu Ala His Ala Phe
  180         185         190
Pro Pro Gly Pro Gly Ile Gln Gly Asp Ala His Phe Asp Asp Asp Glu
  195         200         205
Leu Trp Ser Leu Gly Lys Gly Val Val Val Pro Thr Arg Phe Gly Asn
  210         215         220
Ala Asp Gly Ala Ala Cys His Phe Pro Phe Ile Phe Glu Gly Arg Ser
  225         230         235         240
Tyr Ser Ala Cys Thr Asp Gly Arg Ser Asp Gly Leu Pro Trp Cys
  245         250         255
Ser Thr Thr Ala Asn Tyr Asp Thr Asp Asp Arg Phe Gly Phe Cys Pro
  260         265         270

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Ser Glu Arg Leu Tyr Thr Arg Asp Gly Asn Ala Asp Gly Lys Pro Cys  
           275                                  280                  285  
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           290                                  295                  300  
 Asp Gly Arg Ser Asp Gly Tyr Arg Trp Cys Ala Thr Thr Ala Asn Tyr  
 305                                  310                  315                  320  
 Asp Arg Asp Lys Leu Phe Gly Phe Cys Pro Thr Arg Ala Asp Ser Thr  
                                   325                  330                  335  
 Val Met Gly Gly Asn Ser Ala Gly Glu Leu Cys Val Phe Pro Phe Thr  
                                   340                  345                  350  
 Phe Leu Gly Lys Glu Tyr Ser Thr Cys Thr Ser Glu Gly Arg Gly Asp  
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 Gly Arg Leu Trp Cys Ala Thr Thr Ser Asn Phe Asp Ser Asp Lys Lys  
                                   370                  375                  380  
 Trp Gly Phe Cys Pro Asp Gln Gly Tyr Ser Leu Phe Leu Val Ala Ala  
 385                                  390                  395                  400  
 His Glu Phe Gly His Ala Leu Gly Leu Asp His Ser Ser Val Pro Glu  
                                   405                  410                  415  
 Ala Leu Met Tyr Pro Met Tyr Arg Phe Thr Glu Gly Pro Pro Leu His  
                                   420                  425                  430  
 Lys Asp Asp Val Asn Gly Ile Arg His Leu Tyr Gly Pro Arg Pro Glu  
                                   435                  440                  445  
 Pro Glu Pro Arg Pro Pro Thr Thr Thr Thr Pro Gln Pro Thr Ala Pro  
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 Pro Thr Val Cys Pro Thr Gly Pro Pro Thr Val His Pro Ser Glu Arg  
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 Pro Thr Ala Gly Pro Thr Gly Pro Pro Ser Ala Gly Pro Thr Gly Pro  
                                   485                  490                  495  
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                                   500                  505                  510  
 Asp Asp Ala Cys Asn Val Asn Ile Phe Asp Ala Ile Ala Glu Ile Gly  
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 Asn Gln Leu Tyr Leu Phe Lys Asp Gly Lys Tyr Trp Arg Phe Ser Glu  
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 Gly Arg Gly Ser Arg Pro Gln Gly Pro Phe Leu Ile Ala Asp Lys Trp  
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 Pro Ala Leu Pro Arg Lys Leu Asp Ser Val Phe Glu Glu Pro Leu Ser  
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 Lys Lys Leu Phe Phe Phe Ser Gly Arg Gln Val Trp Val Tyr Thr Gly  
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 Ala Ser Val Leu Gly Pro Arg Arg Leu Asp Lys Leu Gly Leu Gly Ala  
                                   595                  600                  605  
 Asp Val Ala Gln Val Thr Gly Ala Leu Arg Ser Gly Arg Gly Lys Met  
                                   610                  615                  620  
 Leu Leu Phe Ser Gly Arg Arg Leu Trp Arg Phe Asp Val Lys Ala Gln  
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 Met Val Asp Pro Arg Ser Ala Ser Glu Val Asp Arg Met Phe Pro Gly  
                                   645                  650                  655  
 Val Pro Leu Asp Thr His Asp Val Phe Gln Tyr Arg Glu Lys Ala Tyr  
                                   660                  665                  670  
 Phe Cys Gln Asp Arg Phe Tyr Trp Arg Val Ser Ser Arg Ser Glu Leu  
                                   675                  680                  685  
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 Pro Glu Asp  
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<211> 2217  
 <212> DNA  
 <213> Homo sapiens

<400> 143  
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 <212> PRT  
 <213> Homo sapiens

<400> 144  
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 Asp Gly Val Leu Ala Asn Pro Pro Asn Ile Ser Ser Leu Ser Pro Arg  
 50 55 60  
 Gln Leu Leu Gly Phe Pro Cys Ala Glu Val Ser Gly Leu Ser Thr Glu  
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&lt;210&gt; 145

&lt;211&gt; 2135

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 145

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<211> 630

<212> PRT

<213> Homo sapiens

<400> 146

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&lt;210&gt; 147

&lt;211&gt; 2105

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 147

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&lt;210&gt; 148

&lt;211&gt; 620

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 148

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Met Ala Leu Pro Thr Ala Arg Pro Leu Leu Gly Ser Cys Gly Thr Pro
  1          5          10          15
Ala Leu Gly Ser Leu Leu Phe Leu Leu Phe Ser Leu Gly Trp Val Gln
          20          25          30
Pro Ser Arg Thr Leu Ala Gly Glu Thr Gly Gln Glu Ala Ala Pro Leu
          35          40          45
Asp Gly Val Leu Ala Asn Pro Pro Asn Ile Ser Ser Leu Ser Pro Arg
          50          55          60
Gln Leu Leu Gly Phe Pro Cys Ala Glu Val Ser Gly Leu Ser Thr Glu
          65          70          75          80
Arg Val Arg Glu Leu Ala Val Ala Leu Ala Gln Lys Asn Val Lys Leu
          85          90          95
Ser Thr Glu Gln Leu Arg Cys Leu Ala His Arg Leu Ser Glu Pro Pro
          100          105          110
Glu Asp Leu Asp Ala Leu Pro Leu Asp Leu Leu Leu Phe Leu Asn Pro
          115          120          125
Asp Ala Phe Ser Gly Pro Gln Ala Cys Thr Arg Phe Phe Ser Arg Ile
          130          135          140
Thr Lys Ala Asn Val Asp Leu Leu Pro Arg Gly Ala Pro Glu Arg Gln
          145          150          155          160
Arg Leu Leu Pro Ala Ala Leu Ala Cys Trp Gly Val Arg Gly Ser Leu
          165          170          175
Leu Ser Glu Ala Asp Val Arg Ala Leu Gly Gly Leu Ala Cys Asp Leu
          180          185          190
Pro Gly Arg Phe Val Ala Glu Ser Ala Glu Val Leu Leu Pro Arg Leu
          195          200          205
Val Ser Cys Pro Gly Pro Leu Asp Gln Asp Gln Gln Glu Ala Ala Arg
          210          215          220
Ala Ala Leu Gln Gly Gly Gly Pro Pro Tyr Gly Pro Pro Ser Thr Trp
          225          230          235          240
Ser Val Ser Thr Met Asp Ala Leu Arg Gly Leu Leu Pro Val Leu Gly
          245          250          255
Gln Pro Ile Ile Arg Ser Ile Pro Gln Gly Ile Val Ala Ala Trp Arg
          260          265          270
Gln Arg Ser Ser Arg Asp Pro Ser Trp Arg Gln Pro Glu Arg Thr Ile

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275	280	285
Leu Arg Pro Arg Phe Arg Arg Glu Val Glu Lys Thr Ala Cys Pro Ser		
290	295	300
Gly Lys Lys Ala Arg Glu Ile Asp Glu Ser Leu Ile Phe Tyr Lys Lys		
305	310	315
Trp Glu Leu Glu Ala Cys Val Asp Ala Ala Leu Leu Ala Thr Gln Met		
325	330	335
Asp Arg Val Asn Ala Ile Pro Phe Thr Tyr Glu Gln Leu Asp Val Leu		
340	345	350
Lys His Lys Leu Asp Glu Leu Tyr Pro Gln Gly Tyr Pro Glu Ser Val		
355	360	365
Ile Gln His Leu Gly Tyr Leu Phe Leu Lys Met Ser Pro Glu Asp Ile		
370	375	380
Arg Lys Trp Asn Val Thr Ser Leu Glu Thr Leu Lys Ala Leu Leu Glu		
385	390	395
Val Asn Lys Gly His Glu Met Ser Pro Gln Ala Pro Arg Arg Pro Leu		
405	410	415
Pro Gln Val Ala Thr Leu Ile Asp Arg Phe Val Lys Gly Arg Gly Gln		
420	425	430
Leu Asp Lys Asp Thr Leu Asp Thr Leu Thr Ala Phe Tyr Pro Gly Tyr		
435	440	445
Leu Cys Ser Leu Ser Pro Glu Glu Leu Ser Ser Val Pro Pro Ser Ser		
450	455	460
Ile Trp Ala Val Arg Pro Gln Asp Leu Asp Thr Cys Asp Pro Arg Gln		
465	470	475
Leu Asp Val Leu Tyr Pro Lys Ala Arg Leu Ala Phe Gln Asn Met Asn		
485	490	495
Gly Ser Glu Tyr Phe Val Lys Ile Gln Ser Phe Leu Gly Gly Ala Pro		
500	505	510
Thr Glu Asp Leu Lys Ala Leu Ser Gln Gln Asn Val Ser Met Asp Leu		
515	520	525
Ala Thr Phe Met Lys Leu Arg Thr Asp Ala Val Leu Pro Leu Thr Val		
530	535	540
Ala Glu Val Gln Lys Leu Leu Gly Pro His Val Glu Gly Leu Lys Ala		
545	550	555
Glu Glu Arg His Arg Pro Val Arg Asp Trp Ile Leu Arg Gln Arg Gln		
565	570	575
Asp Asp Leu Asp Thr Leu Gly Leu Gly Leu Gln Gly Gly Ile Pro Asn		
580	585	590
Gly Tyr Leu Val Leu Asp Leu Ser Val Gln Gly Pro Gly Pro Val Leu		
595	600	605
Thr Val Leu Ala Leu Leu Leu Ala Ser Thr Leu Ala		
610	615	620

&lt;210&gt; 149

&lt;211&gt; 2193

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 149

```

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cctccctccc tgggatctac acagaccatg gccttgccaa cggctcgacc cctgttgggg 120
tctgtgggga ccccgccct cggcagcctc ctgttcctgc tcttcagcct cggatgggtg 180
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gcggaggtgt ccggcctgag cacggagcgt gtccgggagc tggctgtggc cttggcacag 360
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cccgaggacc tggacgccct cccattggac ctgctgctat tcctcaacc agatgcgttc 480

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gcagacacgt aaaaaaaaaa aaaaaaaaaa aaa 2193

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&lt;210&gt; 150

&lt;211&gt; 694

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 150

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Met Ala Leu Pro Thr Ala Arg Pro Leu Leu Gly Ser Cys Gly Thr Pro
1          5          10          15
Ala Leu Gly Ser Leu Leu Phe Leu Leu Phe Ser Leu Gly Trp Val Gln
20          25          30
Pro Ser Arg Thr Leu Ala Gly Glu Thr Gly Gln Glu Ala Ala Pro Leu
35          40          45
Asp Gly Val Leu Ala Asn Pro Pro Asn Ile Ser Ser Leu Ser Pro Arg
50          55          60
Gln Leu Leu Gly Phe Pro Cys Ala Glu Val Ser Gly Leu Ser Thr Glu
65          70          75          80
Arg Val Arg Glu Leu Ala Val Ala Leu Ala Gln Lys Asn Val Lys Leu
85          90          95
Ser Thr Glu Gln Leu Arg Cys Leu Ala His Arg Leu Ser Glu Pro Pro
100         105         110
Glu Asp Leu Asp Ala Leu Pro Leu Asp Leu Leu Leu Phe Leu Asn Pro
115         120         125
Asp Ala Phe Ser Gly Pro Gln Ala Cys Thr Arg Phe Phe Ser Arg Ile
130         135         140
Thr Lys Ala Asn Val Asp Leu Leu Pro Arg Gly Ala Pro Glu Arg Gln
145         150         155         160
Arg Leu Leu Pro Ala Ala Leu Ala Cys Trp Gly Val Arg Gly Ser Leu
165         170         175
Leu Ser Glu Ala Asp Val Arg Ala Leu Gly Gly Leu Ala Cys Asp Leu

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			180					185					190				
Pro	Gly	Arg	Phe	Val	Ala	Glu	Ser	Ala	Glu	Val	Leu	Leu	Pro	Arg	Leu		
			195						200						205		
Val	Ser	Cys	Pro	Gly	Pro	Leu	Asp	Gln	Asp	Gln	Gln	Glu	Ala	Ala	Arg		
			210						215						220		
Ala	Ala	Leu	Gln	Gly	Gly	Gly	Pro	Pro	Tyr	Gly	Pro	Pro	Ser	Thr	Trp		
225			230						235						240		
Ser	Val	Ser	Thr	Met	Asp	Ala	Leu	Arg	Gly	Leu	Leu	Pro	Val	Leu	Gly		
			245						250						255		
Gln	Pro	Ile	Ile	Arg	Ser	Ile	Pro	Gln	Gly	Ile	Val	Ala	Ala	Trp	Arg		
			260						265						270		
Gln	Arg	Ser	Ser	Arg	Asp	Pro	Ser	Trp	Arg	Gln	Pro	Glu	Arg	Thr	Ile		
			275						280						285		
Leu	Arg	Pro	Arg	Phe	Arg	Arg	Glu	Val	Glu	Lys	Thr	Ala	Cys	Pro	Ser		
			290						295						300		
Gly	Lys	Lys	Ala	Arg	Glu	Ile	Asp	Glu	Ser	Leu	Ile	Phe	Tyr	Lys	Lys		
305			310						315						320		
Trp	Glu	Leu	Glu	Ala	Cys	Val	Asp	Ala	Ala	Leu	Leu	Ala	Thr	Gln	Met		
			325						330						335		
Asp	Arg	Val	Asn	Ala	Ile	Pro	Phe	Thr	Tyr	Glu	Gln	Leu	Asp	Val	Leu		
			340						345						350		
Lys	His	Lys	Leu	Asp	Glu	Leu	Tyr	Pro	Gln	Gly	Tyr	Pro	Glu	Ser	Val		
			355						360						365		
Ile	Gln	His	Leu	Gly	Tyr	Leu	Phe	Leu	Lys	Met	Ser	Pro	Glu	Asp	Ile		
			370						375						380		
Arg	Lys	Trp	Asn	Val	Thr	Ser	Leu	Glu	Thr	Leu	Lys	Ala	Leu	Leu	Glu		
385			390						395						400		
Val	Asn	Lys	Gly	His	Glu	Met	Ser	Pro	Gln	Val	Ala	Thr	Leu	Ile	Asp		
			405						410						415		
Arg	Phe	Val	Lys	Gly	Arg	Gly	Gln	Leu	Asp	Lys	Asp	Thr	Leu	Asp	Thr		
			420						425						430		
Leu	Thr	Ala	Phe	Tyr	Pro	Gly	Tyr	Leu	Cys	Ser	Leu	Ser	Pro	Glu	Glu		
			435						440						445		
Leu	Ser	Ser	Val	Pro	Pro	Ser	Ser	Ile	Trp	Ala	Val	Arg	Pro	Gln	Asp		
			450						455						460		
Leu	Asp	Thr	Cys	Asp	Pro	Arg	Gln	Leu	Asp	Val	Leu	Tyr	Pro	Lys	Ala		
465			470						475						480		
Arg	Leu	Ala	Phe	Gln	Asn	Met	Asn	Gly	Ser	Glu	Tyr	Phe	Val	Lys	Ile		
			485						490						495		
Gln	Ser	Phe	Leu	Gly	Gly	Ala	Pro	Thr	Glu	Asp	Leu	Lys	Ala	Leu	Ser		
			500						505						510		
Gln	Gln	Asn	Val	Ser	Met	Asp	Leu	Ala	Thr	Phe	Met	Lys	Leu	Arg	Thr		
			515						520						525		
Asp	Ala	Val	Leu	Pro	Leu	Thr	Val	Ala	Glu	Val	Gln	Lys	Leu	Leu	Gly		
			530						535						540		
Pro	His	Val	Glu	Gly	Leu	Lys	Ala	Glu	Glu	Arg	His	Arg	Pro	Val	Arg		
545			550						555						560		
Asp	Trp	Ile	Leu	Arg	Gln	Arg	Gln	Asp	Asp	Leu	Asp	Thr	Leu	Gly	Leu		
			565						570						575		
Gly	Leu	Gln	Gly	Gly	Ile	Pro	Asn	Gly	Tyr	Leu	Val	Leu	Asp	Leu	Ser		
			580						585						590		

Trp Pro Gln Pro Cys Trp Gly Ser Pro Pro Gly Gln Glu Gln Ala Arg  
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 Val Ile Pro Val Pro Pro Gln Glu Asn Ser Arg Ser Val Asn Gly Asn  
 675 680 685  
 Met Pro Pro Ala Asp Thr  
 690

<210> 151  
 <211> 2081  
 <212> DNA  
 <213> Homo sapiens

<400> 151  
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<210> 152  
 <211> 612  
 <212> PRT  
 <213> Homo sapiens

<400> 152  
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 Ala Leu Gly Ser Leu Leu Phe Leu Leu Phe Ser Leu Gly Trp Val Gln





Gln Ser Phe Leu Gly Gly Ala Pro Thr Glu Asp Leu Lys Ala Leu Ser  
 500 505 510  
 Gln Gln Asn Val Ser Met Asp Leu Ala Thr Phe Met Lys Leu Arg Thr  
 515 520 525  
 Asp Ala Val Leu Pro Leu Thr Val Ala Glu Val Gln Lys Leu Leu Gly  
 530 535 540  
 Pro His Val Glu Gly Leu Lys Ala Glu Glu Arg His Arg Pro Val Arg  
 545 550 555 560  
 Asp Trp Ile Leu Arg Gln Arg Gln Asp Asp Leu Asp Thr Leu Gly Leu  
 565 570 575  
 Gly Leu Gln Gly Gly Ile Pro Asn Gly Tyr Leu Val Leu Asp Leu Ser  
 580 585 590  
 Val Gln Gly Pro Gly Pro Val Leu Thr Val Leu Ala Leu Leu Leu Ala  
 595 600 605  
 Ser Thr Leu Ala  
 610

&lt;210&gt; 153

&lt;211&gt; 2111

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 153

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aaaaaaaaa a

2111

&lt;210&gt; 154

&lt;211&gt; 622

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 154

```

Met Ala Leu Pro Thr Ala Arg Pro Leu Leu Gly Ser Cys Gly Thr Pro
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Ala Leu Gly Ser Leu Leu Phe Leu Leu Phe Ser Leu Gly Trp Val Gln
          20          25          30
Pro Ser Arg Thr Leu Ala Gly Glu Thr Gly Gln Glu Ala Ala Pro Leu
          35          40          45
Asp Gly Val Leu Ala Asn Pro Pro Asn Ile Ser Ser Leu Ser Pro Arg
 50          55          60
Gln Leu Leu Gly Phe Pro Cys Ala Glu Val Ser Gly Leu Ser Thr Glu
65          70          75          80
Arg Val Arg Glu Leu Ala Val Ala Leu Ala Gln Lys Asn Val Lys Leu
          85          90          95
Ser Thr Glu Gln Leu Arg Cys Leu Ala His Arg Leu Ser Glu Pro Pro
          100          105          110
Glu Asp Leu Asp Ala Leu Pro Leu Asp Leu Leu Leu Phe Leu Asn Pro
          115          120          125
Asp Ala Phe Ser Gly Pro Gln Ala Cys Thr Arg Phe Phe Ser Arg Ile
          130          135          140
Thr Lys Ala Asn Val Asp Leu Leu Pro Arg Gly Ala Pro Glu Arg Gln
          145          150          155          160
Arg Leu Leu Pro Ala Ala Leu Ala Cys Trp Gly Val Arg Gly Ser Leu
          165          170          175
Leu Ser Glu Ala Asp Val Arg Ala Leu Gly Gly Leu Ala Cys Asp Leu
          180          185          190
Pro Gly Arg Phe Val Ala Glu Ser Ala Glu Val Leu Leu Pro Arg Leu
          195          200          205
Val Ser Cys Pro Gly Pro Leu Asp Gln Asp Gln Gln Glu Ala Ala Arg
          210          215          220
Ala Ala Leu Gln Gly Gly Gly Pro Pro Tyr Gly Pro Pro Ser Thr Trp
          225          230          235          240
Ser Val Ser Thr Met Asp Ala Leu Arg Gly Leu Leu Pro Val Leu Gly
          245          250          255
Gln Pro Ile Ile Arg Ser Ile Pro Gln Gly Ile Val Ala Ala Trp Arg
          260          265          270
Gln Arg Ser Ser Arg Asp Pro Ser Trp Arg Gln Pro Glu Arg Thr Ile
          275          280          285
Leu Arg Pro Arg Phe Arg Arg Glu Val Glu Lys Thr Ala Cys Pro Ser
          290          295          300
Gly Lys Lys Ala Arg Glu Ile Asp Glu Ser Leu Ile Phe Tyr Lys Lys
          305          310          315          320
Trp Glu Leu Glu Ala Cys Val Asp Ala Ala Leu Leu Ala Thr Gln Met
          325          330          335
Asp Arg Val Asn Ala Ile Pro Phe Thr Tyr Glu Gln Leu Asp Val Leu
          340          345          350
Lys His Lys Leu Asp Glu Leu Tyr Pro Gln Gly Tyr Pro Glu Ser Val
          355          360          365
Ile Gln His Leu Gly Tyr Leu Phe Leu Lys Met Ser Pro Glu Asp Ile
          370          375          380
Arg Lys Trp Asn Val Thr Ser Leu Glu Thr Leu Lys Ala Leu Leu Glu
          385          390          395          400
Val Asn Lys Gly His Glu Met Ser Pro Gln Val Ala Thr Leu Ile Asp

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<210> 155
<211> 1721
<212> DNA
<213> Homo sapiens
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agaagtttcag	tgcccagctc	tactgagaag	aatgtctgtga	gtatgaccag	cagcgtactc	240	
tcacggccaaca	gcccggttcc	aggctcctcc	accactcagg	gacaggatgt	cacctctggcc	300	
ccggccacagg	aaccagcttc	aggttcagct	gccacctggg	gacaggatgt	cacctcgggtc	360	
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acctaccatc ctatgagcga gtaccccacc taccacaccc atgggcgcta tgtgcccct 1500
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tcttacacaa acccagcagt ggcagccact tctgccaact tgtaggggca cgtcgccctc 1620
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ctgggagccc ccaccacaac acttcccagg catggaattc c 1721

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&lt;210&gt; 156

&lt;211&gt; 515

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 156

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Met Thr Pro Gly Thr Gln Ser Pro Phe Phe Leu Leu Leu Leu Leu Thr
 1          5          10          15
Val Leu Thr Val Val Thr Gly Ser Gly His Ala Ser Ser Thr Pro Gly
 20          25          30
Gly Glu Lys Glu Thr Ser Ala Thr Gln Arg Ser Ser Val Pro Ser Ser
 35          40          45
Thr Glu Lys Asn Ala Val Ser Met Thr Ser Ser Val Leu Ser Ser His
 50          55          60
Ser Pro Gly Ser Gly Ser Ser Thr Thr Gln Gly Gln Asp Val Thr Leu
 65          70          75          80
Ala Pro Ala Thr Glu Pro Ala Ser Gly Ser Ala Ala Thr Trp Gly Gln
 85          90          95
Asp Val Thr Ser Val Pro Val Thr Arg Pro Ala Leu Gly Ser Thr Thr
100          105          110
Pro Pro Ala His Asp Val Thr Ser Ala Pro Asp Asn Lys Pro Ala Pro
115          120          125
Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr
130          135          140
Arg Pro Pro Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser
145          150          155          160
Ala Pro Asp Thr Arg Pro Pro Pro Gly Ser Thr Ala Pro Ala Ala His
165          170          175
Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala
180          185          190
Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Asn Arg Pro Ala Leu
195          200          205
Ala Ser Thr Ala Pro Pro Val His Asn Val Thr Ser Ala Ser Gly Ser
210          215          220
Ala Ser Gly Ser Ala Ser Thr Leu Val His Asn Gly Thr Ser Ala Arg
225          230          235          240
Ala Thr Thr Thr Pro Ala Ser Lys Ser Thr Pro Phe Ser Ile Pro Ser
245          250          255
His His Ser Asp Thr Pro Thr Thr Leu Ala Ser His Ser Thr Lys Thr
260          265          270
Asp Ala Ser Ser Thr His His Ser Thr Val Pro Pro Leu Thr Ser Ser
275          280          285
Asn His Ser Thr Ser Pro Gln Leu Ser Thr Gly Val Ser Phe Phe Phe
290          295          300
Leu Ser Phe His Ile Ser Asn Leu Gln Phe Asn Ser Ser Leu Glu Asp
305          310          315          320
Pro Ser Thr Asp Tyr Tyr Gln Glu Leu Gln Arg Asp Ile Ser Glu Met
325          330          335
Phe Leu Gln Ile Tyr Lys Gln Gly Gly Phe Leu Gly Leu Ser Asn Ile
340          345          350
Lys Phe Arg Pro Gly Ser Val Val Val Gln Leu Thr Leu Ala Phe Arg
355          360          365
Glu Gly Thr Ile Asn Val His Asp Val Glu Thr Gln Phe Asn Gln Tyr

```

370		375		380
Lys Thr Glu Ala Ala Ser Arg Tyr Asn Leu Thr Ile Ser Asp Val Ser				
385		390		395
Val Ser Asp Val Pro Phe Pro Phe Ser Ala Gln Ser Gly Ala Gly Val				400
	405		410	415
Pro Gly Trp Gly Ile Ala Leu Leu Val Leu Val Cys Val Leu Val Ala				
	420		425	430
Leu Ala Ile Val Tyr Leu Ile Ala Leu Ala Val Cys Gln Cys Arg Arg				
	435		440	445
Lys Asn Tyr Gly Gln Leu Asp Ile Phe Pro Ala Arg Asp Thr Tyr His				
	450		455	460
Pro Met Ser Glu Tyr Pro Thr Tyr His Thr His Gly Arg Tyr Val Pro				
465		470		475
Pro Ser Ser Thr Asp Arg Ser Pro Tyr Glu Lys Val Ser Ala Gly Asn				
	485		490	495
Gly Gly Ser Ser Leu Ser Tyr Thr Asn Pro Ala Val Ala Ala Thr Ser				
	500		505	510
Ala Asn Leu				
515				

&lt;210&gt; 157

&lt;211&gt; 4139

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 157

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gacttcggct	accagagaa	gttcagtgcc	cagctctact	gagaagaatg	ctgtgagtat	240
gaccagcagc	gtactctcca	gccacagccc	cggttcaggc	tcctccacca	ctcagggaca	300
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cgatgtcacc	tcagcccccg	acaacaagcc	agccccgggc	tcaccgccc	ccccagccca	480
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&lt;210&gt; 158

&lt;211&gt; 1255

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 158

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 20          25          30
Gly Glu Lys Glu Thr Ser Ala Thr Gln Arg Ser Ser Val Pro Ser Ser
 35          40          45
Thr Glu Lys Asn Ala Val Ser Met Thr Ser Ser Val Leu Ser Ser His
 50          55          60
Ser Pro Gly Ser Gly Ser Ser Thr Thr Gln Gly Gln Asp Val Thr Leu
 65          70          75          80
Ala Pro Ala Thr Glu Pro Ala Ser Gly Ser Ala Ala Thr Trp Gly Gln
 85          90          95
Asp Val Thr Ser Val Pro Val Thr Arg Pro Ala Leu Gly Ser Thr Thr
100          105          110
Pro Pro Ala His Asp Val Thr Ser Ala Pro Asp Asn Lys Pro Ala Pro

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Arg 145	Pro	Ala	Pro	Gly	Ser 150	Thr	Ala	Pro	Pro	Ala 155	His	Gly	Val	Thr	Ser 160
Ala	Pro	Asp	Thr	Arg 165	Pro	Ala	Pro	Gly	Ser 170	Thr	Ala	Pro	Pro	Ala 175	His
Gly	Val	Thr	Ser 180	Ala	Pro	Asp	Thr	Arg 185	Pro	Ala	Pro	Gly	Ser 190	Thr	Ala
Pro	Pro	Ala	His 195	Gly	Val	Thr	Ser 200	Ala	Pro	Asp	Thr	Arg 205	Pro	Ala	Pro
Gly	Ser 210	Thr	Ala	Pro	Pro	Ala 215	His	Gly	Val	Thr	Ser 220	Ala	Pro	Asp	Thr
Arg 225	Pro	Ala	Pro	Gly	Ser 230	Thr	Ala	Pro	Pro	Ala 235	His	Gly	Val	Thr	Ser 240
Ala	Pro	Asp	Thr	Arg 245	Pro	Ala	Pro	Gly	Ser 250	Thr	Ala	Pro	Pro	Ala 255	His
Gly	Val	Thr	Ser 260	Ala	Pro	Asp	Thr	Arg 265	Pro	Ala	Pro	Gly	Ser 270	Thr	Ala
Pro	Pro	Ala 275	His	Gly	Val	Thr	Ser 280	Ala	Pro	Asp	Thr	Arg 285	Pro	Ala	Pro
Gly	Ser 290	Thr	Ala	Pro	Pro	Ala 295	His	Gly	Val	Thr	Ser 300	Ala	Pro	Asp	Thr
Arg 305	Pro	Ala	Pro	Gly	Ser 310	Thr	Ala	Pro	Pro	Ala 315	His	Gly	Val	Thr	Ser 320
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Pro	Pro	Ala 355	His	Gly	Val	Thr	Ser 360	Ala	Pro	Asp	Thr	Arg 365	Pro	Ala	Pro
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Arg 385	Pro	Ala	Pro	Gly	Ser 390	Thr	Ala	Pro	Pro	Ala 395	His	Gly	Val	Thr	Ser 400
Ala	Pro	Asp	Thr	Arg 405	Pro	Ala	Pro	Gly	Ser 410	Thr	Ala	Pro	Pro	Ala 415	His
Gly	Val	Thr	Ser 420	Ala	Pro	Asp	Thr	Arg 425	Pro	Ala	Pro	Gly	Ser 430	Thr	Ala
Pro	Pro	Ala 435	His	Gly	Val	Thr	Ser 440	Ala	Pro	Asp	Thr	Arg 445	Pro	Ala	Pro
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Arg 465	Pro	Ala	Pro	Gly	Ser 470	Thr	Ala	Pro	Pro	Ala 475	His	Gly	Val	Thr	Ser 480
Ala	Pro	Asp	Thr	Arg 485	Pro	Ala	Pro	Gly	Ser 490	Thr	Ala	Pro	Pro	Ala 495	His
Gly	Val	Thr	Ser 500	Ala	Pro	Asp	Thr	Arg 505	Pro	Ala	Pro	Gly	Ser 510	Thr	Ala
Pro	Pro	Ala 515	His	Gly	Val	Thr	Ser 520	Ala	Pro	Asp	Thr	Arg 525	Pro	Ala	Pro
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Arg 545	Pro	Ala	Pro	Gly	Ser 550	Thr	Ala	Pro	Pro	Ala 555	His	Gly	Val	Thr	Ser 560
Ala	Pro	Asp	Thr	Arg 565	Pro	Ala	Pro	Gly	Ser 570	Thr	Ala	Pro	Pro	Ala 575	His
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Arg	Pro	Ala	Pro	Gly	Ser	Thr	Ala	Pro	Pro	Ala	His	Gly	Val	Thr	Ser
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Ala	Pro	Asp	Thr	Arg	Pro	Ala	Pro	Gly	Ser	Thr	Ala	Pro	Pro	Ala	His
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Gly	Val	Thr	Ser	Ala	Pro	Asp	Thr	Arg	Pro	Ala	Pro	Gly	Ser	Thr	Ala
							660					665			670
Pro	Pro	Ala	His	Gly	Val	Thr	Ser	Ala	Pro	Asp	Thr	Arg	Pro	Ala	Pro
							675					680			685
Gly	Ser	Thr	Ala	Pro	Pro	Ala	His	Gly	Val	Thr	Ser	Ala	Pro	Asp	Thr
							690					695			700
Arg	Pro	Ala	Pro	Gly	Ser	Thr	Ala	Pro	Pro	Ala	His	Gly	Val	Thr	Ser
							705					710			715
Ala	Pro	Asp	Thr	Arg	Pro	Ala	Pro	Gly	Ser	Thr	Ala	Pro	Pro	Ala	His
							720					725			730
Gly	Val	Thr	Ser	Ala	Pro	Asp	Thr	Arg	Pro	Ala	Pro	Gly	Ser	Thr	Ala
							735					740			745
Pro	Pro	Ala	His	Gly	Val	Thr	Ser	Ala	Pro	Asp	Thr	Arg	Pro	Ala	Pro
							750					755			760
Gly	Ser	Thr	Ala	Pro	Pro	Ala	His	Gly	Val	Thr	Ser	Ala	Pro	Asp	Thr
							765					770			775
Arg	Pro	Ala	Pro	Gly	Ser	Thr	Ala	Pro	Pro	Ala	His	Gly	Val	Thr	Ser
							780					785			790
Ala	Pro	Asp	Thr	Arg	Pro	Ala	Pro	Gly	Ser	Thr	Ala	Pro	Pro	Ala	His
							795					800			805
Gly	Val	Thr	Ser	Ala	Pro	Asp	Thr	Arg	Pro	Ala	Pro	Gly	Ser	Thr	Ala
							810					815			820
Pro	Pro	Ala	His	Gly	Val	Thr	Ser	Ala	Pro	Asp	Thr	Arg	Pro	Ala	Pro
							825					830			835
Gly	Ser	Thr	Ala	Pro	Pro	Ala	His	Gly	Val	Thr	Ser	Ala	Pro	Asp	Thr
							840					845			850
Arg	Pro	Ala	Pro	Gly	Ser	Thr	Ala	Pro	Pro	Ala	His	Gly	Val	Thr	Ser
							855					860			865
Ala	Pro	Asp	Thr	Arg	Pro	Ala	Pro	Gly	Ser	Thr	Ala	Pro	Pro	Ala	His
							870					875			880
Gly	Val	Thr	Ser	Ala	Pro	Asp	Thr	Arg	Pro	Ala	Pro	Gly	Ser	Thr	Ala
							885					890			895
Pro	Pro	Ala	His	Gly	Val	Thr	Ser	Ala	Pro	Asp	Thr	Arg	Pro	Ala	Pro
							900					905			910
Gly	Ser	Thr	Ala	Pro	Pro	Ala	His	Gly	Val	Thr	Ser	Ala	Pro	Asp	Asn
							915					920			925
Arg	Pro	Ala	Leu	Gly	Ser	Thr	Ala	Pro	Pro	Val	His	Asn	Val	Thr	Ser
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Ala	Ser	Gly	Ser	Ala	Ser	Gly	Ser	Ala	Ser	Thr	Leu	Val	His	Asn	Gly
							945					950			955
Thr	Ser	Ala	Arg	Ala	Thr	Thr	Thr	Pro	Ala	Ser	Lys	Ser	Thr	Pro	Phe
							960					965			970
Ser	Ile	Pro	Ser	His	His	Ser	Asp	Thr	Pro	Thr	Thr	Leu	Ala	Ser	His
							975					980			985
Ser	Thr	Lys	Thr	Asp	Ala	Ser	Ser	Thr	His	His	Ser	Ser	Val	Pro	Pro
							990					995			1000
Leu	Thr	Ser	Ser	Asn	His	Ser	Thr	Ser	Pro	Gln	Leu	Ser	Thr	Gly	Val
							1005					1010			1015
Ser	Phe	Phe	Phe	Leu	Ser	Phe	His	Ile	Ser	Asn	Leu	Gln	Phe	Asn	Ser
							1020					1025			1030
Ser	Leu	Glu	Asp	Pro	Ser	Thr	Asp	Tyr	Tyr	Gln	Glu	Leu	Gln	Arg	Asp
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							1045					1050			1055



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Leu	Ala	Phe	Arg	Glu	Gly	Thr	Ile	Asn	Val	His	Asp	Val	Glu	Thr	Gln	
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Val	Leu	Val	Ala	Leu	Ala	Ile	Val	Tyr	Leu	Ile	Ala	Leu	Ala	Val	Cys	
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Gln	Cys	Arg	Arg	Lys	Asn	Tyr	Gly	Gln	Leu	Asp	Ile	Phe	Pro	Ala	Arg	
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Arg	Tyr	Val	Pro	Pro	Ser	Ser	Thr	Asp	Arg	Ser	Pro	Tyr	Glu	Lys	Val	
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&lt;210&gt; 159

&lt;211&gt; 2627

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 159

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&lt;210&gt; 160

&lt;211&gt; 700

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 160

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 35          40          45
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 50          55          60
Thr Asp Gln Gln Cys Gln Tyr Arg Trp Leu Arg Val Leu Asn Pro Asp
 65          70          75          80
Leu Val Lys Gly Pro Trp Thr Lys Glu Glu Asp Gln Lys Val Ile Glu
 85          90          95
Leu Val Lys Lys Tyr Gly Thr Lys Gln Trp Thr Leu Ile Ala Lys His
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Leu Lys Gly Arg Leu Gly Lys Gln Cys Arg Glu Arg Trp His Asn His
115          120          125
Leu Asn Pro Glu Val Lys Lys Ser Cys Trp Thr Glu Glu Glu Asp Arg
130          135          140
Ile Ile Cys Glu Ala His Lys Val Leu Gly Asn Arg Trp Ala Glu Ile
145          150          155          160
Ala Lys Met Leu Pro Gly Arg Thr Asp Asn Ala Val Lys Asn His Trp
165          170          175
Asn Ser Thr Ile Lys Arg Lys Val Asp Thr Gly Gly Phe Leu Ser Glu
180          185          190
Ser Lys Asp Cys Lys Pro Pro Val Tyr Leu Leu Leu Glu Leu Glu Asp
195          200          205
Lys Asp Gly Leu Gln Ser Ala Gln Pro Thr Glu Gly Gln Gly Ser Leu
210          215          220
Leu Thr Asn Trp Pro Ser Val Pro Pro Thr Ile Lys Glu Glu Glu Asn
225          230          235          240
Ser Glu Glu Glu Leu Ala Ala Thr Thr Ser Lys Glu Gln Glu Pro
245          250          255
Ile Gly Thr Asp Leu Asp Ala Val Arg Thr Pro Glu Pro Leu Glu Glu
260          265          270

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Phe Pro Lys Arg Glu Asp Gln Glu Gly Ser Pro Pro Glu Thr Ser Leu
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305      310      315      320
Ala Trp Cys Asp Leu Ser Lys Phe Asp Leu Pro Glu Glu Pro Ser Ala
      325      330      335
Glu Asp Ser Ile Asn Asn Ser Leu Val Gln Leu Gln Ala Ser His Gln
      340      345      350
Gln Gln Val Leu Pro Pro Arg Gln Pro Ser Ala Leu Val Pro Ser Val
      355      360      365
Thr Glu Tyr Arg Leu Asp Gly His Thr Ile Ser Asp Leu Ser Arg Ser
      370      375      380
Ser Arg Gly Glu Leu Ile Pro Ile Ser Pro Ser Thr Glu Val Gly Gly
385      390      395      400
Ser Gly Ile Gly Thr Pro Pro Ser Val Leu Lys Arg Gln Arg Lys Arg
      405      410      415
Arg Val Ala Leu Ser Pro Val Thr Glu Asn Ser Thr Ser Leu Ser Phe
      420      425      430
Leu Asp Ser Cys Asn Ser Leu Thr Pro Lys Ser Thr Pro Val Lys Thr
      435      440      445
Leu Pro Phe Ser Pro Ser Gln Phe Leu Asn Phe Trp Asn Lys Gln Asp
      450      455      460
Thr Leu Glu Leu Glu Ser Pro Ser Leu Thr Ser Thr Pro Val Cys Ser
465      470      475      480
Gln Lys Val Val Val Thr Thr Pro Leu His Arg Asp Lys Thr Pro Leu
      485      490      495
His Gln Lys His Ala Ala Phe Val Thr Pro Asp Gln Lys Tyr Ser Met
      500      505      510
Asp Asn Thr Pro His Thr Pro Thr Pro Phe Lys Asn Ala Leu Glu Lys
      515      520      525
Tyr Gly Pro Leu Lys Pro Leu Pro Gln Thr Pro His Leu Glu Glu Asp
      530      535      540
Leu Lys Glu Val Leu Arg Ser Glu Ala Gly Ile Glu Leu Ile Ile Glu
545      550      555      560
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      565      570      575
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      580      585      590
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      610      615      620
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625      630      635      640
Glu Lys Ala Ala Val Ala Gln Lys Pro Arg Ser His Phe Thr Thr Pro
      645      650      655
Ala Pro Met Ser Ser Ala Trp Lys Thr Val Ala Cys Gly Gly Thr Arg
      660      665      670
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Lys Pro Ser His Thr Ser Arg Thr Leu Ile Leu Ser
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<210> 161  
 <211> 6861  
 <212> DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 161

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<210> 162  
 <211> 1972  
 <212> PRT  
 <213> Homo sapiens

<400> 162

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Lys	His	Leu	Pro	Ile	Tyr	Ser	Glu	Lys	Ile	Val	Asp	Met	Tyr	Lys	Gly
	130					135					140				
Lys	Lys	Arg	His	Glu	Met	Pro	Pro	His	Ile	Tyr	Ala	Ile	Ala	Asp	Thr
145					150					155					160
Ala	Tyr	Arg	Ser	Met	Leu	Gln	Asp	Arg	Glu	Asp	Gln	Ser	Ile	Leu	Cys
				165					170					175	
Thr	Gly	Glu	Ser	Gly	Ala	Gly	Lys	Thr	Glu	Asn	Thr	Lys	Lys	Val	Ile
			180					185						190	
Gln	Tyr	Leu	Ala	Val	Val	Ala	Ser	Ser	His	Lys	Gly	Lys	Lys	Asp	Thr
		195					200					205			
Ser	Ile	Thr	Gly	Glu	Leu	Glu	Lys	Gln	Leu	Leu	Gln	Ala	Asn	Pro	Ile
	210					215					220				
Leu	Glu	Ala	Phe	Gly	Asn	Ala	Lys	Thr	Val	Lys	Asn	Asp	Asn	Ser	Ser
225					230					235					240
Arg	Phe	Gly	Lys	Phe	Ile	Arg	Ile	Asn	Phe	Asp	Val	Thr	Gly	Tyr	Ile
				245					250					255	
Val	Gly	Ala	Asn	Ile	Glu	Thr	Tyr	Leu	Leu	Glu	Lys	Ser	Arg	Ala	Ile
			260					265					270		
Arg	Gln	Ala	Arg	Asp	Glu	Arg	Thr	Phe	His	Ile	Phe	Tyr	Tyr	Met	Ile
		275					280					285			
Ala	Gly	Ala	Lys	Glu	Lys	Met	Arg	Ser	Asp	Leu	Leu	Leu	Glu	Gly	Phe
	290					295					300				
Asn	Asn	Tyr	Thr	Phe	Leu	Ser	Asn	Gly	Phe	Val	Pro	Ile	Pro	Ala	Ala
305					310					315					320
Gln	Asp	Asp	Glu	Met	Phe	Gln	Glu	Thr	Val	Glu	Ala	Met	Ala	Ile	Met
				325					330					335	
Gly	Phe	Ser	Glu	Glu	Glu	Gln	Leu	Ser	Ile	Leu	Lys	Val	Val	Ser	Ser
			340					345					350		
Val	Leu	Gln	Leu	Gly	Asn	Ile	Val	Phe	Lys	Lys	Glu	Arg	Asn	Thr	Asp
		355					360					365			
Gln	Ala	Ser	Met	Pro	Asp	Asn	Thr	Ala	Ala	Gln	Lys	Val	Cys	His	Leu
	370					375					380				
Met	Gly	Ile	Asn	Val	Thr	Asp	Phe	Thr	Arg	Ser	Ile	Leu	Thr	Pro	Arg
385					390					395					400
Ile	Lys	Val	Gly	Arg	Asp	Val	Val	Gln	Lys	Ala	Gln	Thr	Lys	Glu	Gln
				405					410					415	

Ala	Asp	Phe	Ala	Val	Glu	Ala	Leu	Ala	Lys	Ala	Thr	Tyr	Glu	Arg	Leu
			420					425					430		
Phe	Arg	Trp	Ile	Leu	Thr	Arg	Val	Asn	Lys	Ala	Leu	Asp	Lys	Thr	His
		435					440					445			
Arg	Gln	Gly	Ala	Ser	Phe	Leu	Gly	Ile	Leu	Asp	Ile	Ala	Gly	Phe	Glu
		450				455					460				
Ile	Phe	Glu	Val	Asn	Ser	Phe	Glu	Gln	Leu	Cys	Ile	Asn	Tyr	Thr	Asn
465				470						475					480
Glu	Lys	Leu	Gln	Gln	Leu	Phe	Asn	His	Thr	Met	Phe	Ile	Leu	Glu	Gln
			485						490					495	
Glu	Glu	Tyr	Gln	Arg	Glu	Gly	Ile	Glu	Trp	Asn	Phe	Ile	Asp	Phe	Gly
			500					505					510		
Leu	Asp	Leu	Gln	Pro	Cys	Ile	Glu	Leu	Ile	Glu	Arg	Pro	Asn	Asn	Pro
		515					520					525			
Pro	Gly	Val	Leu	Ala	Leu	Leu	Asp	Glu	Glu	Cys	Trp	Phe	Pro	Lys	Ala
		530				535					540				
Thr	Asp	Lys	Ser	Phe	Val	Glu	Lys	Leu	Cys	Thr	Glu	Gln	Gly	Ser	His
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Pro	Lys	Phe	Gln	Lys	Pro	Lys	Gln	Leu	Lys	Asp	Lys	Thr	Glu	Phe	Ser
			565						570					575	
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		580						585					590		
Thr	Lys	Asn	Met	Asp	Pro	Leu	Asn	Asp	Asn	Val	Thr	Ser	Leu	Leu	Asn
		595					600					605			
Ala	Ser	Ser	Asp	Lys	Phe	Val	Ala	Asp	Leu	Trp	Lys	Asp	Val	Asp	Arg
		610				615					620				
Ile	Val	Gly	Leu	Asp	Gln	Met	Ala	Lys	Met	Thr	Glu	Ser	Ser	Leu	Pro
625				630						635					640
Ser	Ala	Ser	Lys	Thr	Lys	Lys	Gly	Met	Phe	Arg	Thr	Val	Gly	Gln	Leu
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Tyr	Lys	Glu	Gln	Leu	Gly	Lys	Leu	Met	Thr	Thr	Leu	Arg	Asn	Thr	Thr
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Phe	Gln	Glu	Phe	Arg	Gln	Arg	Tyr	Glu	Ile	Leu	Ala	Ala	Asn	Ala	Ile
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		740						745					750		
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		755					760					765			
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		770				775					780				
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785				790						795					800
Leu	Ala	Arg	Lys	Ala	Phe	Ala	Lys	Arg	Gln	Gln	Gln	Leu	Thr	Ala	Met
			805						810					815	
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Gln	Trp	Trp	Arg	Leu	Phe	Thr	Lys	Val	Lys	Pro	Leu	Leu	Gln	Val	Thr
		835					840					845			
Arg	Gln	Glu	Glu	Glu	Met	Gln	Ala	Lys	Glu	Asp	Glu	Leu	Gln	Lys	Thr
		850				855					860				
Lys	Glu	Arg	Gln	Gln	Lys	Ala	Glu	Asn	Glu	Leu	Lys	Glu	Leu	Glu	Gln
865				870						875					880
Lys	His	Ser	Gln	Leu	Thr	Glu	Glu	Lys	Asn	Leu	Leu	Gln	Glu	Gln	Leu

885							890				895				
Gln	Ala	Glu	Thr	Glu	Leu	Tyr	Ala	Glu	Ala	Glu	Glu	Met	Arg	Val	Arg
900							905				910				
Leu	Ala	Ala	Lys	Lys	Gln	Glu	Leu	Glu	Glu	Ile	Leu	His	Glu	Met	Glu
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Ala	Arg	Leu	Glu	Glu	Glu	Glu	Asp	Arg	Gly	Gln	Gln	Leu	Gln	Ala	Glu
930							935				940				
Arg	Lys	Lys	Met	Ala	Gln	Met	Leu	Asp	Leu	Glu	Glu	Gln	Leu	Glu	
945							950				955				
Glu	Glu	Glu	Ala	Ala	Arg	Gln	Lys	Leu	Gln	Leu	Glu	Lys	Val	Thr	Ala
965							970				975				
Glu	Ala	Lys	Ile	Lys	Lys	Leu	Glu	Asp	Glu	Ile	Leu	Val	Met	Asp	Asp
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Gln	Asn	Asn	Lys	Leu	Ser	Lys	Glu	Arg	Lys	Leu	Leu	Glu	Glu	Arg	Ile
995							1000				1005				
Ser	Asp	Leu	Thr	Thr	Asn	Leu	Ala	Glu	Glu	Glu	Glu	Lys	Ala	Lys	Asn
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Lys	Arg	Lys	Leu	Glu	Gly	Asp	Ala	Ser	Asp	Phe	His	Glu	Gln	Ile	Ala
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1075							1080				1085				
Glu	Glu	Glu	Leu	Gln	Ala	Ala	Leu	Ala	Arg	Leu	Asp	Asp	Glu	Ile	Ala
1090							1095				1100				
Gln	Lys	Asn	Asn	Ala	Leu	Lys	Lys	Ile	Arg	Glu	Leu	Glu	Gly	His	Ile
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Ser	Asp	Leu	Gln	Glu	Asp	Leu	Asp	Ser	Glu	Arg	Ala	Ala	Arg	Asn	Lys
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Ala	Glu	Lys	Gln	Lys	Arg	Asp	Leu	Gly	Glu	Glu	Leu	Glu	Ala	Leu	Lys
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Thr	Glu	Leu	Glu	Asp	Thr	Leu	Asp	Ser	Thr	Ala	Thr	Gln	Gln	Glu	Leu
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1170							1175				1180				
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1345							1350				1355				
											1360				



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 1380 1385 1390  
 Gly Lys Lys Arg Phe Gln Lys Glu Ile Glu Asn Leu Thr Gln Gln Tyr  
 1395 1400 1405  
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1825                      1830                      1835                      1840  
 Thr Lys Ser Leu Lys Gln Lys Asp Lys Lys Leu Lys Glu Ile Leu Leu  
                                  1845                      1850                      1855  
 Gln Val Glu Asp Glu Arg Lys Met Ala Glu Gln Tyr Lys Glu Gln Ala  
                                  1860                      1865                      1870  
 Glu Lys Gly Asn Ala Arg Val Lys Gln Leu Lys Arg Gln Leu Glu Glu  
                                  1875                      1880                      1885  
 Ala Glu Glu Glu Ser Gln Arg Ile Asn Ala Asn Arg Arg Lys Leu Gln  
                                  1890                      1895                      1900  
 Arg Glu Leu Asp Glu Ala Thr Glu Ser Asn Glu Ala Met Gly Arg Glu  
 1905                      1910                      1915                      1920  
 Val Asn Ala Leu Lys Ser Lys Leu Arg Arg Gly Asn Glu Thr Ser Phe  
                                  1925                      1930                      1935  
 Val Pro Ser Arg Arg Ser Gly Gly Arg Arg Val Ile Glu Asn Ala Asp  
                                  1940                      1945                      1950  
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 Lys Ala Ser Glu  
 1970

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&lt;211&gt; 6900

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 163

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&lt;210&gt; 164

&lt;211&gt; 1938

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 164

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Lys Arg Leu Val Trp Val Pro Ser Glu Lys Gln Gly Phe Glu Ala Ala
      35           40           45
Ser Ile Lys Glu Glu Lys Gly Asp Glu Val Val Val Glu Leu Val Glu
      50           55           60
Asn Gly Lys Lys Val Thr Val Gly Lys Asp Asp Ile Gln Lys Met Asn
      65           70           75           80
Pro Pro Lys Phe Ser Lys Val Glu Asp Met Ala Glu Leu Thr Cys Leu
      85           90           95
Asn Glu Ala Ser Val Leu His Asn Leu Arg Glu Arg Tyr Phe Ser Gly
      100          105          110
Leu Ile Tyr Thr Tyr Ser Gly Leu Phe Cys Val Val Val Asn Pro Tyr
      115          120          125
Lys His Leu Pro Ile Tyr Ser Glu Lys Ile Val Asp Met Tyr Lys Gly
      130          135          140
Lys Lys Arg His Glu Met Pro Pro His Ile Tyr Ala Ile Ala Asp Thr
      145          150          155          160
Ala Tyr Arg Ser Met Leu Gln Asp Arg Glu Asp Gln Ser Ile Leu Cys
      165          170          175
Thr Gly Glu Ser Gly Ala Gly Lys Thr Glu Asn Thr Lys Lys Val Ile
      180          185          190
Gln Tyr Leu Ala Val Val Ala Ser Ser His Lys Gly Lys Lys Asp Thr
      195          200          205
Ser Ile Thr Gly Glu Leu Glu Lys Gln Leu Leu Gln Ala Asn Pro Ile

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Leu Glu Ala Phe Gly	Asn Ala Lys Thr Val	Lys Asn Asp Asn Ser Ser
225	230	235
Arg Phe Gly Lys Phe	Ile Arg Ile Asn Phe	Asp Val Thr Gly Tyr Ile
	245	250
Val Gly Ala Asn Ile	Glu Thr Tyr Leu Leu	Glu Lys Ser Arg Ala Ile
	260	265
Arg Gln Ala Arg Asp	Glu Arg Thr Phe His	Ile Phe Tyr Tyr Met Ile
	275	280
Ala Gly Ala Lys Glu	Lys Met Arg Ser Asp	Leu Leu Leu Glu Gly Phe
	290	295
Asn Asn Tyr Thr Phe	Leu Ser Asn Gly Phe	Val Pro Ile Pro Ala Ala
305	310	315
Gln Asp Asp Glu Met	Phe Gln Glu Thr Val	Glu Ala Met Ala Ile Met
	325	330
Gly Phe Ser Glu Glu	Gln Leu Ser Ile Leu	Lys Val Val Ser Ser
	340	345
Val Leu Gln Leu Gly	Asn Ile Val Phe Lys	Lys Glu Arg Asn Thr Asp
	355	360
Gln Ala Ser Met Pro	Asp Asn Thr Ala Ala	Gln Lys Val Cys His Leu
	370	375
Met Gly Ile Asn Val	Thr Asp Phe Thr Arg	Ser Ile Leu Thr Pro Arg
385	390	395
Ile Lys Val Gly Arg	Asp Val Val Gln Lys	Ala Gln Thr Lys Glu Gln
	405	410
Ala Asp Phe Ala Val	Glu Ala Leu Ala Lys	Ala Thr Tyr Glu Arg Leu
	420	425
Phe Arg Trp Ile Leu	Thr Arg Val Asn Lys	Ala Leu Asp Lys Thr His
	435	440
Arg Gln Gly Ala Ser	Phe Leu Gly Ile Leu	Asp Ile Ala Gly Phe Glu
	450	455
Ile Phe Glu Val Asn	Ser Phe Glu Gln Leu	Cys Ile Asn Tyr Thr Asn
465	470	475
Glu Lys Leu Gln Gln	Leu Phe Asn His Thr	Met Phe Ile Leu Glu Gln
	485	490
Glu Glu Tyr Gln Arg	Glu Gly Ile Glu Trp	Asn Phe Ile Asp Phe Gly
	500	505
Leu Asp Leu Gln Pro	Cys Ile Glu Leu Ile	Glu Arg Pro Asn Asn Pro
	515	520
Pro Gly Val Leu Ala	Leu Leu Asp Glu Glu	Cys Trp Phe Pro Lys Ala
	530	535
Thr Asp Lys Ser Phe	Val Glu Lys Leu Cys	Thr Glu Gln Gly Ser His
545	550	555
Pro Lys Phe Gln Lys	Pro Lys Gln Leu Lys	Asp Lys Thr Glu Phe Ser
	565	570
Ile Ile His Tyr Ala	Gly Lys Val Asp Tyr	Asn Ala Ser Ala Trp Leu
	580	585
Thr Lys Asn Met Asp	Pro Leu Asn Asp Asn	Val Thr Ser Leu Leu Asn
	595	600
Ala Ser Ser Asp Lys	Phe Val Ala Asp Leu	Trp Lys Asp Val Asp Arg
	610	615
Ile Val Gly Leu Asp	Gln Met Ala Lys Met	Thr Glu Ser Ser Leu Pro
625	630	635
Ser Ala Ser Lys Thr	Lys Lys Gly Met Phe	Arg Thr Val Gly Gln Leu
	645	650
Tyr Lys Glu Gln Leu	Gly Lys Leu Met Thr	Thr Leu Arg Asn Thr Thr
	660	665
Pro Asn Phe Val Arg	Cys Ile Ile Pro Asn	His Glu Lys Arg Ser Gly
	675	680
		685

Lys	Leu	Asp	Ala	Phe	Leu	Val	Leu	Glu	Gln	Leu	Arg	Cys	Asn	Gly	Val
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Leu	Glu	Gly	Ile	Arg	Ile	Cys	Arg	Gln	Gly	Phe	Pro	Asn	Arg	Ile	Val
705					710					715					720
Phe	Gln	Glu	Phe	Arg	Gln	Arg	Tyr	Glu	Ile	Leu	Ala	Ala	Asn	Ala	Ile
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Pro	Lys	Gly	Phe	Met	Asp	Gly	Lys	Gln	Ala	Cys	Ile	Leu	Met	Ile	Lys
			740					745					750		
Ala	Leu	Glu	Leu	Asp	Pro	Asn	Leu	Tyr	Arg	Ile	Gly	Gln	Ser	Lys	Ile
			755				760					765			
Phe	Phe	Arg	Thr	Gly	Val	Leu	Ala	His	Leu	Glu	Glu	Glu	Arg	Asp	Leu
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Lys	Ile	Thr	Asp	Val	Ile	Met	Ala	Phe	Gln	Ala	Met	Cys	Arg	Gly	Tyr
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Leu	Ala	Arg	Lys	Ala	Phe	Ala	Lys	Arg	Gln	Gln	Gln	Leu	Thr	Ala	Met
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Lys	Val	Ile	Gln	Arg	Asn	Cys	Ala	Ala	Tyr	Leu	Lys	Leu	Arg	Asn	Trp
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Gln	Trp	Trp	Arg	Leu	Phe	Thr	Lys	Val	Lys	Pro	Leu	Leu	Gln	Val	Thr
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Arg	Gln	Glu	Glu	Glu	Met	Gln	Ala	Lys	Glu	Asp	Glu	Leu	Gln	Lys	Thr
	850					855					860				
Lys	Glu	Arg	Gln	Gln	Lys	Ala	Glu	Asn	Glu	Leu	Lys	Glu	Leu	Glu	Gln
865					870					875					880
Lys	His	Ser	Gln	Leu	Thr	Glu	Glu	Lys	Asn	Leu	Leu	Gln	Glu	Gln	Leu
				885					890					895	
Gln	Ala	Glu	Thr	Glu	Leu	Tyr	Ala	Glu	Ala	Glu	Glu	Met	Arg	Val	Arg
			900					905					910		
Leu	Ala	Ala	Lys	Lys	Gln	Glu	Leu	Glu	Glu	Ile	Leu	His	Glu	Met	Glu
			915				920					925			
Ala	Arg	Leu	Glu	Glu	Glu	Glu	Asp	Arg	Gly	Gln	Gln	Leu	Gln	Ala	Glu
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Arg	Lys	Lys	Met	Ala	Gln	Gln	Met	Leu	Asp	Leu	Glu	Glu	Gln	Leu	Glu
945					950					955					960
Glu	Glu	Glu	Ala	Ala	Arg	Gln	Lys	Leu	Gln	Leu	Glu	Lys	Val	Thr	Ala
				965					970					975	
Glu	Ala	Lys	Ile	Lys	Lys	Leu	Glu	Asp	Glu	Ile	Leu	Val	Met	Asp	Asp
			980					985					990		
Gln	Asn	Asn	Lys	Leu	Ser	Lys	Glu	Arg	Lys	Leu	Leu	Glu	Glu	Arg	Ile
			995				1000					1005			
Ser	Asp	Leu	Thr	Thr	Asn	Leu	Ala	Glu	Glu	Glu	Glu	Lys	Ala	Lys	Asn
	1010					1015						1020			
Leu	Thr	Lys	Leu	Lys	Asn	Lys	His	Glu	Ser	Met	Ile	Ser	Glu	Leu	Glu
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Val	Arg	Leu	Lys	Lys	Glu	Glu	Lys	Ser	Arg	Gln	Glu	Leu	Glu	Lys	Leu
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Lys	Arg	Lys	Leu	Glu	Gly	Asp	Ala	Ser	Asp	Phe	His	Glu	Gln	Ile	Ala
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Asp	Leu	Gln	Ala	Gln	Ile	Ala	Glu	Leu	Lys	Met	Gln	Leu	Ala	Lys	Lys
	1075						1080					1085			
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	1090					1095					1100				
Gln	Lys	Asn	Asn	Ala	Leu	Lys	Lys	Ile	Arg	Glu	Leu	Glu	Gly	His	Ile
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Ser	Asp	Leu	Gln	Glu	Asp	Leu	Asp	Ser	Glu	Arg	Ala	Ala	Arg	Asn	Lys
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Ala	Glu	Lys	Gln	Lys	Arg	Asp	Leu	Gly	Glu	Glu	Leu	Glu	Ala	Leu	Lys
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Thr	Glu	Leu	Glu	Asp	Thr	Leu	Asp	Ser	Thr	Ala	Thr	Gln	Gln	Glu	Leu

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Glu Glu Thr Arg Ser His	Glu Ala Gln Val Gln Glu Met Arg Gln Lys	
1185	1190	1195
His Ala Gln Ala Val Glu Glu Leu Thr	Glu Gln Leu Glu Gln Phe Lys	1200
1205	1210	1215
Arg Ala Lys Ala Asn Leu Asp Lys	Asn Lys Gln Thr Leu Glu Lys Glu	
1220	1225	1230
Asn Ala Asp Leu Ala Gly Glu Leu Arg Val Leu Gly Gln Ala Lys Gln		
1235	1240	1245
Glu Val Glu His Lys Lys Lys Lys Leu Glu Ala Gln Val Gln Glu Leu		
1250	1255	1260
Gln Ser Lys Cys Ser Asp Gly Glu Arg Ala Arg Ala Glu Leu Asn Asp		
1265	1270	1275
Lys Val His Lys Leu Gln Asn Glu Val Glu Ser Val Thr Gly Met Leu		
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Asn Glu Ala Glu Gly Lys Ala Ile Lys Leu Ala Lys Asp Val Ala Ser		
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Leu Ser Ser Gln Leu Gln Asp Thr Gln Glu Leu Leu Gln Glu Glu Thr		
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Arg Gln Lys Leu Asn Val Ser Thr Lys Leu Arg Gln Leu Glu Glu Glu		
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Arg Asn Ser Leu Gln Asp Gln Leu Asp Glu Glu Met Glu Ala Lys Gln		
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Gly Lys Lys Arg Phe Gln Lys Glu Ile Glu Asn Leu Thr Gln Gln Tyr		
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Ala Arg Ala Leu Glu Glu Ala Leu Glu Ala Lys Glu Glu Leu Glu Arg		
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Thr Asn Lys Met Leu Lys Ala Glu Met Glu Asp Leu Val Ser Ser Lys		
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Asp Asp Val Gly Lys Asn Val His Glu Leu Glu Lys Ser Lys Arg Ala		
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Leu Glu Thr Gln Met Glu Glu Met Lys Thr Gln Leu Glu Glu Leu Glu		
1540	1545	1550
Asp Glu Leu Gln Ala Thr Glu Asp Ala Lys Leu Arg Leu Glu Val Asn		
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Met Gln Ala Leu Lys Gly Gln Phe Glu Arg Asp Leu Gln Ala Arg Asp		
1570	1575	1580
Glu Gln Asn Glu Glu Lys Arg Arg Gln Leu Gln Arg Gln Leu His Glu		
1585	1590	1595
Tyr Glu Thr Glu Leu Glu Asp Glu Arg Lys Gln Arg Ala Leu Ala Ala		
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1620	1625	1630

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 1665 1670 1675 1680  
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 Thr Lys Ser Leu Lys Gln Lys Asp Lys Lys Leu Lys Glu Ile Leu Leu  
 1845 1850 1855  
 Gln Val Glu Asp Glu Arg Lys Met Ala Glu Gln Tyr Lys Glu Gln Ala  
 1860 1865 1870  
 Glu Lys Gly Asn Ala Arg Val Lys Gln Leu Lys Arg Gln Leu Glu Glu  
 1875 1880 1885  
 Ala Glu Glu Glu Ser Gln Arg Ile Asn Ala Asn Arg Arg Lys Leu Gln  
 1890 1895 1900  
 Arg Glu Leu Asp Glu Ala Thr Glu Ser Asn Glu Ala Met Gly Arg Glu  
 1905 1910 1915 1920  
 Val Asn Ala Leu Lys Ser Lys Leu Arg Gly Pro Pro Pro Gln Glu Thr  
 1925 1930 1935  
 Ser Gln

&lt;210&gt; 165

&lt;211&gt; 958

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 165

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<210> 166

<211> 234

<212> PRT

<213> Homo sapiens

<400> 166

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Val	Ser	Ala	Cys	Asp	Thr	Glu	Asp	Thr	Val	Gly	His	Leu	Gly	Pro	Trp
	35						40					45			
Arg	Asp	Lys	Asp	Pro	Ala	Leu	Trp	Cys	Gln	Leu	Cys	Leu	Ser	Ser	Gln
	50					55					60				
His	Gln	Ala	Ile	Glu	Arg	Phe	Tyr	Asp	Lys	Met	Gln	Asn	Ala	Glu	Ser
65					70				75					80	
Gly	Arg	Gly	Gln	Val	Met	Ser	Ser	Leu	Ala	Glu	Leu	Glu	Asp	Asp	Phe
			85						90				95		
Lys	Glu	Gly	Tyr	Leu	Glu	Thr	Val	Ala	Ala	Tyr	Tyr	Glu	Glu	Gln	His
		100						105					110		
Pro	Glu	Leu	Thr	Pro	Leu	Leu	Glu	Lys	Glu	Arg	Asp	Gly	Leu	Arg	Cys
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Glu	Pro	Gly	Glu	Ser	Phe	Cys	Asx	Lys	Val	Met	Arg	Trp	Phe	Gln	Ala
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			165						170					175	
Lys	Glu	Lys	Val	Val	Ala	Leu	Val	His	Ala	Val	Gln	Ala	Leu	Trp	Lys
		180						185					190		
Gln	Phe	Gln	Ser	Phe	Cys	Cys	Ser	Leu	Ser	Glu	Leu	Phe	Met	Ser	Ser
	195						200					205			
Phe	Gln	Ser	Tyr	Gly	Ala	Pro	Arg	Gly	Asp	Lys	Glu	Glu	Leu	Thr	Pro
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<210> 167

<211> 958

<212> DNA

<213> Homo sapiens

<400> 167

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 tctcttcaca gcaccaggcc atagaaaagat tttatgataa aatgcaaaat gcagaatcag 300  
 gacgtggaca ggtgatgtcg agcctggcag agctggagga cgacttcaaa gagggctacc 360  
 tggagacagt ggcggcttat tatgaggagc agcaccacaga gctcactcct ctacttgaaa 420  
 aagaaagaga tggattacgg tgccgaggca acagatcccc tgtcccggat gttgaggatc 480  
 ccgcaaccga ggagcctggg gagagctttt gtgacaaggt catgagatgg ttccaggcca 540

```

tgctgcagcg gctgcagacc tgggtggcacg gggttctggc ctgggtgaag gagaagggtgg 600
tggccctggg ccatgcagtg caggccctct ggaaacagtt ccagagtttc tgctgctctc 660
tgtcagagct cttcatgtcc tctttccagt cctacggagc cccacggggg gacaaggagg 720
agctgacacc ccagaagtgc tctgaacccc aatcctcaaa atgaagatac tgacaccacc 780
tttgcctctc ccgtcaccgc gcaccacccc tgaccctctc ctcagctgtc ctgtgccccg 840
ccctctcccg cacactcagt ccccctgcct ggcgttcctg ccgcagctct gacctgggtgc 900
tgtcgcctcg gcatcttaat aaaacctgct tatacttccc tggcagggag ataccatg 958

```

&lt;210&gt; 168

&lt;211&gt; 234

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 168

```

Met Cys Phe Pro Lys Val Leu Ser Asp Asp Met Lys Lys Leu Lys Ala
1      5      10      15
Arg Met Val Met Leu Leu Pro Thr Ser Ala Gln Gly Leu Gly Ala Trp
20     25     30
Val Ser Ala Cys Asp Thr Glu Asp Thr Val Gly His Leu Gly Pro Trp
35     40     45
Arg Asp Lys Asp Pro Ala Leu Trp Cys Gln Leu Cys Leu Ser Ser Gln
50     55     60
His Gln Ala Ile Glu Arg Phe Tyr Asp Lys Met Gln Asn Ala Glu Ser
65     70     75     80
Gly Arg Gly Gln Val Met Ser Ser Leu Ala Glu Leu Glu Asp Asp Phe
85     90     95
Lys Glu Gly Tyr Leu Glu Thr Val Ala Ala Tyr Tyr Glu Glu Gln His
100    105    110
Pro Glu Leu Thr Pro Leu Leu Glu Lys Glu Arg Asp Gly Leu Arg Cys
115    120    125
Arg Gly Asn Arg Ser Pro Val Pro Asp Val Glu Asp Pro Ala Thr Glu
130    135    140
Glu Pro Gly Glu Ser Phe Cys Asp Lys Val Met Arg Trp Phe Gln Ala
145    150    155    160
Met Leu Gln Arg Leu Gln Thr Trp Trp His Gly Val Leu Ala Trp Val
165    170    175
Lys Glu Lys Val Val Ala Leu Val His Ala Val Gln Ala Leu Trp Lys
180    185    190
Gln Phe Gln Ser Phe Cys Cys Ser Leu Ser Glu Leu Phe Met Ser Ser
195    200    205
Phe Gln Ser Tyr Gly Ala Pro Arg Gly Asp Lys Glu Glu Leu Thr Pro
210    215    220
Gln Lys Cys Ser Glu Pro Gln Ser Ser Lys
225    230

```

&lt;210&gt; 169

&lt;211&gt; 1005

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 169

```

tgtgtgtgcta ttgtgtggat gccgcgcgtg tcttctcttc tttccagaga tggctaacag 60
gggccccgagc tatggcttaa gccgagaggt gcaggagaag atcgagcaga agtatgatgc 120
ggacctggag aacaagctgg tggactggat catcctgcag tgcgccgagg acatagagca 180
cccgcccccc ggcagggcc attttcagaa atggttaatg gacgggacgg tcctgtgcaa 240
gctgataaat agtttatacc caccaggaca agagcccata cccaagatct cagagtcaaa 300
gatggctttt aagcagatgg agcaaatctc ccagttccta aaagctgcgg agacctatgg 360
tgtcagaacc accgacatct ttcagacggg ggatctatgg gaagggaagg acatggcagc 420

```

```

tgtgcagagg accctgatgg ctttaggcag cgttgcagtc accaaggatg atggctgcta 480
tcggggagag ccatacctggt ttcacaggaa agcccagcag aatcgagag gcttttccga 540
ggagcagctt cgccagggaac agaacgtaat aggcctgcag atgggcagca acaagggagc 600
ctcccaggcg ggcatagcag ggtacgggat gccacggcag atcatgttag gacgcggcat 660
cctgcccctg gtagagagga cgaatgttcc acaccatggt ctctacgaaa aagaaatagt 720
tagtcacctt ctgaccttct cctctttctc aaagccttct gtccctgggt tttgcaagtg 780
ctgcatttcc gccgagaatc cgcgttgccct actgctgcca cctcctgttc atttagaact 840
atgcaaagac tccgcttccg ttttctgag ctccctcgggc cccagagtct ctgtttgatt 900
atttatttat ttatttattt atttgccaaa aattctctct ttcaacttat agaatgcacc 960
taataaagta attaagtctt gtggaaaaaa aaaaaaaaaa aaaaaa 1005

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&lt;210&gt; 170

&lt;211&gt; 282

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 170

```

Met Ala Asn Arg Gly Pro Ser Tyr Gly Leu Ser Arg Glu Val Gln Glu
 1          5          10          15
Lys Ile Glu Gln Lys Tyr Asp Ala Asp Leu Glu Asn Lys Leu Val Asp
          20          25          30
Trp Ile Ile Leu Gln Cys Ala Glu Asp Ile Glu His Pro Pro Gly
          35          40          45
Arg Ala His Phe Gln Lys Trp Leu Met Asp Gly Thr Val Leu Cys Lys
          50          55          60
Leu Ile Asn Ser Leu Tyr Pro Pro Gly Gln Glu Pro Ile Pro Lys Ile
          65          70          75          80
Ser Glu Ser Lys Met Ala Phe Lys Gln Met Glu Gln Ile Ser Gln Phe
          85          90          95
Leu Lys Ala Ala Glu Thr Tyr Gly Val Arg Thr Thr Asp Ile Phe Gln
          100          105          110
Thr Val Asp Leu Trp Glu Gly Lys Asp Met Ala Ala Val Gln Arg Thr
          115          120          125
Leu Met Ala Leu Gly Ser Val Ala Val Thr Lys Asp Asp Gly Cys Tyr
          130          135          140
Arg Gly Glu Pro Ser Trp Phe His Arg Lys Ala Gln Gln Asn Arg Arg
          145          150          155          160
Gly Phe Ser Glu Glu Gln Leu Arg Gln Gly Gln Asn Val Ile Gly Leu
          165          170          175
Gln Met Gly Ser Asn Lys Gly Ala Ser Gln Ala Gly Met Thr Gly Tyr
          180          185          190
Gly Met Pro Arg Gln Ile Met Leu Gly Arg Gly Ile Leu Pro Leu Val
          195          200          205
Glu Arg Thr Asn Val Pro His His Gly Leu Tyr Glu Lys Glu Ile Val
          210          215          220
Ser His Leu Leu Thr Phe Ser Ser Phe Ser Lys Pro Ser Val Pro Gly
          225          230          235          240
Phe Cys Lys Cys Cys Ile Ser Ala Glu Asn Pro Arg Cys Leu Leu Leu
          245          250          255
Pro Pro Pro Val His Leu Glu Leu Cys Lys Asp Ser Ala Ser Val Phe
          260          265          270
Leu Ser Ser Ser Gly Pro Arg Val Ser Val
          275          280

```

&lt;210&gt; 171

&lt;211&gt; 942

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 171

```

atgagaattg cagtgatttg cttttgcctc ctaggcatca cctgtgccat accagttaaa 60
caggctgatt ctggaagttc tgaggaaaag cagctttaca acaaataccc agatgctgtg 120
gccacatggc taaaccctga cccatctcag aagcagaatc tcctagcccc acagaatgct 180
gtgtcctctg aagaaaccaa tgacttttaa caagagaccc ttccaagtaa gtccaacgaa 240
agccatgacc acatggatga tatggatgat gaagatgatg atgaccatgt ggacagccag 300
gactccattg actcgaacga ctctgatgat gtagatgaca ctgatgattc tcaccagtct 360
gatgagtctc accattctga tgaatctgat gaactgggtc ctgattttcc cacggacctg 420
ccagcaaccg aagttttcac tccagttgtc cccacagtag acacatatga tggccgaggt 480
gatagtgtgg tttatggact gaggtcaaaa tctaagaagt ttcgcagacc tgacatccag 540
taccctgatg ctacagacga gcacatcacc tcacacatgg aaagcgagga gttgaatgg 600
gcatacaagg ccatccccgt tgcccaggac ctgaacgcgc cttctgattg ggacagccgt 660
gggaaggaca gttatgaaac gagtcagctg gatgaccaga gtgctgaagc ccacagccac 720
aagcagtcca gattatataa gcggaaagct aatgatgaga gcaatgagca ttccgatgtg 780
attgatagtc aggaactttc caaagtcagc cgtgaattcc acagccatga atttcacagc 840
catgaagata tgctggttgt agaccccaaa agtaaggaag aagataaaca cctgaaattt 900
cgtatttctc atgaattaga tagtgcactc tctgaggtca at 942

```

&lt;210&gt; 172

&lt;211&gt; 314

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 172

```

Met Arg Ile Ala Val Ile Cys Phe Cys Leu Leu Gly Ile Thr Cys Ala
1           5           10           15
Ile Pro Val Lys Gln Ala Asp Ser Gly Ser Ser Glu Glu Lys Gln Leu
20           25           30
Tyr Asn Lys Tyr Pro Asp Ala Val Ala Thr Trp Leu Asn Pro Asp Pro
35           40           45
Ser Gln Lys Gln Asn Leu Leu Ala Pro Gln Asn Ala Val Ser Ser Glu
50           55           60
Glu Thr Asn Asp Phe Lys Gln Glu Thr Leu Pro Ser Lys Ser Asn Glu
65           70           75           80
Ser His Asp His Met Asp Asp Met Asp Asp Glu Asp Asp Asp Asp His
85           90           95
Val Asp Ser Gln Asp Ser Ile Asp Ser Asn Asp Ser Asp Asp Val Asp
100          105          110
Asp Thr Asp Asp Ser His Gln Ser Asp Glu Ser His His Ser Asp Glu
115          120          125
Ser Asp Glu Leu Val Thr Asp Phe Pro Thr Asp Leu Pro Ala Thr Glu
130          135          140
Val Phe Thr Pro Val Val Pro Thr Val Asp Thr Tyr Asp Gly Arg Gly
145          150          155          160
Asp Ser Val Val Tyr Gly Leu Arg Ser Lys Ser Lys Lys Phe Arg Arg
165          170          175
Pro Asp Ile Gln Tyr Pro Asp Ala Thr Asp Glu His Ile Thr Ser His
180          185          190
Met Glu Ser Glu Glu Leu Asn Gly Ala Tyr Lys Ala Ile Pro Val Ala
195          200          205
Gln Asp Leu Asn Ala Pro Ser Asp Trp Asp Ser Arg Gly Lys Asp Ser
210          215          220
Tyr Glu Thr Ser Gln Leu Asp Asp Gln Ser Ala Glu Ala His Ser His
225          230          235          240
Lys Gln Ser Arg Leu Tyr Lys Arg Lys Ala Asn Asp Glu Ser Asn Glu
245          250          255
His Ser Asp Val Ile Asp Ser Gln Glu Leu Ser Lys Val Ser Arg Glu
260          265          270

```

Phe His Ser His Glu Phe His Ser His Glu Asp Met Leu Val Val Asp  
 275 280 285  
 Pro Lys Ser Lys Glu Glu Asp Lys His Leu Lys Phe Arg Ile Ser His  
 290 295 300  
 Glu Leu Asp Ser Ala Ser Ser Glu Val Asn  
 305 310

<210> 173  
 <211> 1524  
 <212> DNA  
 <213> Homo sapiens

<400> 173  
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 aacgccgacc aaggaaaact cactaccatg agaattgcag tgatttgctt ttgcctccta 120  
 ggcatcacct gtgccatacc agttaaacag gctgattctg gaagttctga ggaaaagcag 180  
 ctttacaaca aatacccaga tgctgtggcc acatggctaa accctgaccc atctcagaag 240  
 cagaatctcc tagccccaca gacccttcca agtaagtcca acgaaagcca tgaccacatg 300  
 gatgatatgg atgatgaaga tgatgatgac catgtggaca gccaggactc cattgactcg 360  
 aacgactctg atgatgtaga tgacactgat gattctcacc agtctgatga gtctcaccat 420  
 tctgatgaat ctgatgaact ggctactgat tttcccacgg acctgccagc aaccgaagtt 480  
 ttcactccag ttgtcccccac agtagacaca tatgatggcc gaggtgatag tgtggtttat 540  
 ggactgaggt caaaatctaa gaagtttcgc agacctgaca tccagtaccc tgatgctaca 600  
 gacgaggaca tcacctcaca catggaaagc gaggagttga atgggtgcata caaggccatc 660  
 cccgttgccc aggacctgaa cgcgccttct gattgggaca gccgtgggaa ggacagttat 720  
 gaaacgagtc agctggatga ccagagtgtt gaaacccaca gccacaagca gtccagatta 780  
 tataagcggg aagccaatga tgagagcaat gagcattccg atgtgattga tagtcaggaa 840  
 ctttccaaag tcagccgtga attccacagc catgaatttc acagccatga agatattgctg 900  
 gttgtagacc ccaaaaagtaa ggaagaagat aaacacctga aatttcgtat ttctcatgaa 960  
 ttagatagtg catcttctga ggtcaattaa aaggagaaaa aatacaattt ctacttttgc 1020  
 atttagtcaa aagaaaaaat gctttatagc aaaatgaaag agaacatgaa atgcttcttt 1080  
 ctgagtttat tgggtgaatg tgtatctatt tgagtctgga aataactaat gtgtttgata 1140  
 attagtttag tttgtggctt catggaaact ccctgtaaac taaaagcttc agggttatgt 1200  
 ctatgttcat tctatagaag aaatgcaaac tatcactgta ttttaatat ttgtattctc 1260  
 tcatgaatag aaatttatgt agaagcaaac aaaatacttt taccactta aaaagagaat 1320  
 ataacatttt atgtcactat aatcttttgt tttttaagtt agtgtatatt ttgttgtgat 1380  
 tatctttttg tgggtggaat aaatctttta tcttgaatgt aataagaatt tgggtggtgc 1440  
 aattgcttat ttgttttccc acggttggtc agcaattaat aaaacataac cttttttact 1500  
 gcctaaaaaa aaaaaaaaaa aaaa 1524

<210> 174  
 <211> 300  
 <212> PRT  
 <213> Homo sapiens

<400> 174  
 Met Arg Ile Ala Val Ile Cys Phe Cys Leu Leu Gly Ile Thr Cys Ala  
 1 5 10 15  
 Ile Pro Val Lys Gln Ala Asp Ser Gly Ser Ser Glu Glu Lys Gln Leu  
 20 25 30  
 Tyr Asn Lys Tyr Pro Asp Ala Val Ala Thr Trp Leu Asn Pro Asp Pro  
 35 40 45  
 Ser Gln Lys Gln Asn Leu Leu Ala Pro Gln Thr Leu Pro Ser Lys Ser  
 50 55 60  
 Asn Glu Ser His Asp His Met Asp Asp Met Asp Glu Asp Asp Asp  
 65 70 75 80  
 Asp His Val Asp Ser Gln Asp Ser Ile Asp Ser Asn Asp Ser Asp Asp  
 85 90 95

```

Val Asp Asp Thr Asp Asp Ser His Gln Ser Asp Glu Ser His His Ser
      100      105      110
Asp Glu Ser Asp Glu Leu Val Thr Asp Phe Pro Thr Asp Leu Pro Ala
      115      120      125
Thr Glu Val Phe Thr Pro Val Val Pro Thr Val Asp Thr Tyr Asp Gly
      130      135      140
Arg Gly Asp Ser Val Val Tyr Gly Leu Arg Ser Lys Ser Lys Lys Phe
      145      150      155      160
Arg Arg Pro Asp Ile Gln Tyr Pro Asp Ala Thr Asp Glu Asp Ile Thr
      165      170      175
Ser His Met Glu Ser Glu Glu Leu Asn Gly Ala Tyr Lys Ala Ile Pro
      180      185      190
Val Ala Gln Asp Leu Asn Ala Pro Ser Asp Trp Asp Ser Arg Gly Lys
      195      200      205
Asp Ser Tyr Glu Thr Ser Gln Leu Asp Asp Gln Ser Ala Glu Thr His
      210      215      220
Ser His Lys Gln Ser Arg Leu Tyr Lys Arg Lys Ala Asn Asp Glu Ser
      225      230      235      240
Asn Glu His Ser Asp Val Ile Asp Ser Gln Glu Leu Ser Lys Val Ser
      245      250      255
Arg Glu Phe His Ser His Glu Phe His Ser His Glu Asp Met Leu Val
      260      265      270
Val Asp Pro Lys Ser Lys Glu Glu Asp Lys His Leu Lys Phe Arg Ile
      275      280      285
Ser His Glu Leu Asp Ser Ala Ser Ser Glu Val Asn
      290      295      300

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&lt;210&gt; 175

&lt;211&gt; 861

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 175

```

atgagaattg cagtgatttg cttttgcctc ctaggcacat cctgtgccat accagttaaa 60
caggctgatt ctggaagttc tgaggaaaag cagaatgctg tgtcctctga agaaaccaat 120
gacttttaaac aagagaccct tccaagtaag tccaacgaaa gccatgacca catggatgat 180
atggatgatg aagatgatga tgaccatgtg gacagccagg actccattga ctcgaacgac 240
tctgatgatg tagatgacac tgatgattct caccagtctg atgagtctca ccattctgat 300
gaatctgatg aactggtcac tgattttccc acggacctgc cagcaaccga agttttcact 360
ccagttgtcc ccacagtaga cacatatgat ggccgagggtg atagtgtggt ttatggactg 420
aggtcaaaat ctaagaagtt tcgcagacct gacatccagt accctgatgc tacagacgag 480
cacatcacct cacacatgga aagcgaggag ttgaatggtg catacaaggc catccccgtt 540
gcccgaggacc tgaacgcgcc ttctgattgg gacagccgtg ggaaggacag ttatgaaacg 600
agtcagctgg atgaccagag tgctgaagcc cacagccaca agcagtccag attatataag 660
cgaaaagcta atgatgagag caatgagcat tccgatgtga ttgatagtca ggaactttcc 720
aaagtcagcc gtgaattcca cagccatgaa ttccacagcc atgaagatat gctggttgta 780
gacccccaaa gtaaggaaga agataaacac ctgaaatttc gtattttctca tgaattagat 840
agtgcattct ctgaggtcaa t                                     861

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&lt;210&gt; 176

&lt;211&gt; 287

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 176

```

Met Arg Ile Ala Val Ile Cys Phe Cys Leu Leu Gly Ile Thr Cys Ala
  1           5           10           15
Ile Pro Val Lys Gln Ala Asp Ser Gly Ser Ser Glu Glu Lys Gln Asn

```

```
<210> 177
<211> 3213
<212> DNA
<213> Homo sapiens
```

<400> 177					
agagactcaa	gatgattccc	tttttacc	tgttttctct	actattgctg	cttattgtta 60
acctataaaa	cgccaacaat	cattatgaca	agatcttg	tcatagtcgt	atcaggggtc 120
gggaccaagg	cccaaagtgc	tgtgcccttc	aacagatttt	gggcacaaaa	aagaaatact 180
tcgacacttg	taagaactgg	tataaaaagt	ccatctgtgg	acagaaaaacg	actgttttat 240
atgaattgttg	ccttggttat	atgagaattg	aaggaatgaa	aggctgccca	gcagcttttg 300
ccattgacca	tgttttatgg	actctggggc	tcgtggggagc	caccacaacg	cagcgctatt 360
ctgacgcctc	aaaactgagg	gaggagatcg	agggaaaggg	atccttcact	tactttgcac 420
cgagtaatga	ggcttgggac	aacttggtatt	ctgatatccg	tagaggtttg	gagagcaacg 480
tgaatgttga	attactgaat	gctttacata	gtcacatgat	taataagaga	atgttgacca 540
aggactttaaa	aaatggcatg	attattcctt	caatgtataa	caatttgggg	cttttcatta 600
accattatcc	taatgggggt	gtcactgtta	attgtgctcg	aatcatccat	gggaaccaga 660
ttgcaacaaa	tggtgttgtc	catgtcattg	accgtgtgct	tacacaaatt	ggtacctcaa 720
ttcaagactt	cattgaagca	gaagatgacc	tttcatcttt	tagagcagct	gccatcacat 780
cggacatatt	ggaggccctt	ggaagagacg	gtcacttcac	actctttgct	cccaccaatg 840
aggcttttga	gaaacttcca	cgagggtgtcc	tagaaagggt	catgggagac	aaagtggctt 900
ccgaagctct	tatgaagtac	cacactctaa	atactctcca	gtgtttctgag	tctatttatgg 960
gaggagcagt	ctttgagacg	ctggaaggaa	atacaattga	gataggatgt	gacggtgaca 1020
gtataacagt	aaatggaatc	aaaatggtga	acaaaaagga	tattgtgaca	aataatggtg 1080

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tgatccattt gattgatcag gtcctaattc ctgattctgc caaacaagtt attgagctgg 1140
ctggaaaaca gcaaaccacc ttcacggatc ttgtggccca attaggcttg gcatctgctc 1200
tgaggccaga tggagaatac actttgctgg cacctgtgaa taatgcattt tctgatgata 1260
ctctcagcat gggttcagcg ctccttaaatt taattctgca gaatcacata ttgaaagtaa 1320
aagttggcct taatgagctt tacaacgggc aaatactgga aaccatcgga ggcaaacagc 1380
tcagagtctt cgtatatcgt acagctgtct gcattgaaaa ttcatgcatg gagaaagggg 1440
gtaagcaagg gagaaacggt gcgattcaca tattccgcga gatcatcaag ccagcagaga 1500
aatccctcca tgaaaagtta aaacaagata agcgctttag caccttcctc agcctacttg 1560
aagctgcaga cttgaaagag ctccctgacac aaacctggaga ctggacatta tttgtgccaa 1620
ccaatgatgc ttttaaggga atgactagag aagaaaaaga aattctgata cgggacaaaa 1680
atgctcttca aaacatcatt ctttatcacc tgacaccagg agttttcatt ggaaaaggat 1740
ttgaacctgg tgttactaac attttaaaga ccacacaagg aagcaaaatc tttctgaaag 1800
aagtaaatac tacacttctg gtgaatgaat tgaaatcaaa agaactctgac atcatgacaa 1860
caaattggtg aattcatggt gtagataaac tcctctatcc agcagacaca cctgttggaa 1920
atgatcaact gctggaaata ctttaataaat taatcaaata catccaaatt aagtttgttc 1980
gtggttagcac cttcaaagaa atccccgtga ctgtctatac aactaaaatt ataaccaaag 2040
ttgtggaacc aaaaatttaa gtgattgaag gcagtcttca gcctattatc aaaactgaag 2100
gacccacact aacaaaagtc aaaattgaag gtgaacctga attcagactg attaaagaag 2160
gtgaaacaat aactgaagtg atccatggag agccaattat taaaaatac accaaaatca 2220
ttgatggagt gcctgtggaa ataactgaaa aagagacacg agaagaacga atcattacag 2280
gtcctgaaat aaaatacact aggatttcta ctggaggtgg agaaacagaa gaaactctga 2340
agaaattggt acaagaagag gtcaccaagg tcaccaaatt cattgaagggt ggtgatggtc 2400
atttatttga agatgaagaa attaaaagac tgcttcaggg agacacaccc gtgaggaagt 2460
tgcaagccaa caaaaaagtt caaggttcta gaagacgatt aaggggaagg cgttctcagt 2520
gaaaatccaa aaaccagaaa aaaatgttta tacaacccta agtcaataac ctgaccttag 2580
aaaattgtga gagccaagtt gacttcagga actgaaacat cagcaciaag aagcaatcat 2640
caaataattc tgaacacaaa tttaatattt tttttctga atgagaaaca tgaggggaaat 2700
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tcactctgac attaaaagtt ctggctaact ttggaatcca ttagagaaaa atccttgtca 2820
ccagattcat tacaattcaa atcgaagagt tgtgaactgt tatcccattg aaaagaccga 2880
gccttgtatg tatgttatgg atacataaaa tgcacgcaag ccattatctc tccatgggaa 2940
gctaagttat aaaaataggt gcttggtgta caaaactttt tatatcaaaa ggctttgcac 3000
atctctatat gagtgggttt actggtaaatt tatgttattt tttacaacta attttgtact 3060
ctcagaatgt ttgtcatatg cttcttgcaa tgcataattt ttaatctcaa acgtttcaat 3120
aaaaccattt ttcagatata aagagaatta cttcaaattg agtaattcag aaaaactcaa 3180
gatttaagtt aaaaagtggt ttggacttgg gaa 3213

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&lt;210&gt; 178

&lt;211&gt; 836

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 178

```

Met Ile Pro Phe Leu Pro Met Phe Ser Leu Leu Leu Leu Leu Ile Val
1           5           10           15
Asn Pro Ile Asn Ala Asn Asn His Tyr Asp Lys Ile Leu Ala His Ser
20           25           30
Arg Ile Arg Gly Arg Asp Gln Gly Pro Asn Val Cys Ala Leu Gln Gln
35           40           45
Ile Leu Gly Thr Lys Lys Lys Tyr Phe Ser Thr Cys Lys Asn Trp Tyr
50           55           60
Lys Lys Ser Ile Cys Gly Gln Lys Thr Thr Val Leu Tyr Glu Cys Cys
65           70           75           80
Pro Gly Tyr Met Arg Met Glu Gly Met Lys Gly Cys Pro Ala Val Leu
85           90           95
Pro Ile Asp His Val Tyr Gly Thr Leu Gly Ile Val Gly Ala Thr Thr
100          105          110
Thr Gln Arg Tyr Ser Asp Ala Ser Lys Leu Arg Glu Glu Ile Glu Gly
115          120          125

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Lys	Gly	Ser	Phe	Thr	Tyr	Phe	Ala	Pro	Ser	Asn	Glu	Ala	Trp	Asp	Asn	130	135	140
Leu	Asp	Ser	Asp	Ile	Arg	Arg	Gly	Leu	Glu	Ser	Asn	Val	Asn	Val	Glu	145	150	155
Leu	Leu	Asn	Ala	Leu	His	Ser	His	Met	Ile	Asn	Lys	Arg	Met	Leu	Thr	165	170	175
Lys	Asp	Leu	Lys	Asn	Gly	Met	Ile	Ile	Pro	Ser	Met	Tyr	Asn	Asn	Leu	180	185	190
Gly	Leu	Phe	Ile	Asn	His	Tyr	Pro	Asn	Gly	Val	Val	Thr	Val	Asn	Cys	195	200	205
Ala	Arg	Ile	Ile	His	Gly	Asn	Gln	Ile	Ala	Thr	Asn	Gly	Val	Val	His	210	215	220
Val	Ile	Asp	Arg	Val	Leu	Thr	Gln	Ile	Gly	Thr	Ser	Ile	Gln	Asp	Phe	225	230	235
Ile	Glu	Ala	Glu	Asp	Leu	Ser	Ser	Phe	Arg	Ala	Ala	Ala	Ile	Thr		245	250	255
Ser	Asp	Ile	Leu	Glu	Ala	Leu	Gly	Arg	Asp	Gly	His	Phe	Thr	Leu	Phe	260	265	270
Ala	Pro	Thr	Asn	Glu	Ala	Phe	Glu	Lys	Leu	Pro	Arg	Gly	Val	Leu	Glu	275	280	285
Arg	Phe	Met	Gly	Asp	Lys	Val	Ala	Ser	Glu	Ala	Leu	Met	Lys	Tyr	His	290	295	300
Ile	Leu	Asn	Thr	Leu	Gln	Cys	Ser	Glu	Ser	Ile	Met	Gly	Gly	Ala	Val	305	310	315
Phe	Glu	Thr	Leu	Glu	Gly	Asn	Thr	Ile	Glu	Ile	Gly	Cys	Asp	Gly	Asp	325	330	335
Ser	Ile	Thr	Val	Asn	Gly	Ile	Lys	Met	Val	Asn	Lys	Lys	Asp	Ile	Val	340	345	350
Thr	Asn	Asn	Gly	Val	Ile	His	Leu	Ile	Asp	Gln	Val	Leu	Ile	Pro	Asp	355	360	365
Ser	Ala	Lys	Gln	Val	Ile	Glu	Leu	Ala	Gly	Lys	Gln	Gln	Thr	Thr	Phe	370	375	380
Thr	Asp	Leu	Val	Ala	Gln	Leu	Gly	Leu	Ala	Ser	Ala	Leu	Arg	Pro	Asp	385	390	395
Gly	Glu	Tyr	Thr	Leu	Ala	Pro	Val	Asn	Asn	Ala	Phe	Ser	Asp	Asp		405	410	415
Thr	Leu	Ser	Met	Val	Gln	Arg	Leu	Leu	Lys	Leu	Ile	Leu	Gln	Asn	His	420	425	430
Ile	Leu	Lys	Val	Lys	Val	Gly	Leu	Asn	Glu	Leu	Tyr	Asn	Gly	Gln	Ile	435	440	445
Leu	Glu	Thr	Ile	Gly	Gly	Lys	Gln	Leu	Arg	Val	Phe	Val	Tyr	Arg	Thr	450	455	460
Ala	Val	Cys	Ile	Glu	Asn	Ser	Cys	Met	Glu	Lys	Gly	Ser	Lys	Gln	Gly	465	470	475
Arg	Asn	Gly	Ala	Ile	His	Ile	Phe	Arg	Glu	Ile	Ile	Lys	Pro	Ala	Glu	485	490	495
Lys	Ser	Leu	His	Glu	Lys	Leu	Lys	Gln	Asp	Lys	Arg	Phe	Ser	Thr	Phe	500	505	510
Leu	Ser	Leu	Glu	Ala	Ala	Asp	Leu	Lys	Glu	Leu	Leu	Thr	Gln	Pro		515	520	525
Gly	Asp	Trp	Thr	Leu	Phe	Val	Pro	Thr	Asn	Asp	Ala	Phe	Lys	Gly	Met	530	535	540
Thr	Ser	Glu	Glu	Lys	Glu	Ile	Leu	Ile	Arg	Asp	Lys	Asn	Ala	Leu	Gln	545	550	555
Asn	Ile	Ile	Leu	Tyr	His	Leu	Thr	Pro	Gly	Val	Phe	Ile	Gly	Lys	Gly	565	570	575
Phe	Glu	Pro	Gly	Val	Thr	Asn	Ile	Leu	Lys	Thr	Thr	Gln	Gly	Ser	Lys	580	585	590
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<210> 179
<211> 3077
<212> DNA
<213> Homo sapiens
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&lt;210&gt; 180

&lt;211&gt; 779

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 180

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20           25           30
Arg Ile Arg Gly Arg Asp Gln Gly Pro Asn Val Cys Ala Leu Gln Gln
35           40           45
Ile Leu Gly Thr Lys Lys Lys Tyr Phe Ser Thr Cys Lys Asn Trp Tyr
50           55           60
Lys Lys Ser Ile Cys Gly Gln Lys Thr Thr Val Leu Tyr Glu Cys Cys
65           70           75           80
Pro Gly Tyr Met Arg Met Glu Gly Met Lys Gly Cys Pro Ala Val Leu
85           90           95
Pro Ile Asp His Val Tyr Gly Thr Leu Gly Ile Val Gly Ala Thr Thr
100          105          110
Thr Gln Arg Tyr Ser Asp Ala Ser Lys Leu Arg Glu Glu Ile Glu Gly
115          120          125
Lys Gly Ser Phe Thr Tyr Phe Ala Pro Ser Asn Glu Ala Trp Asp Asn
130          135          140
Leu Asp Ser Asp Ile Arg Arg Gly Leu Glu Ser Asn Val Asn Val Glu
145          150          155          160

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Lys	Asp	Leu	Lys	Asn	Gly	Met	Ile	Ile	Pro	Ser	Met	Tyr	Asn	Asn	Leu
			180					185					190		
Gly	Leu	Phe	Ile	Asn	His	Tyr	Pro	Asn	Gly	Val	Val	Thr	Val	Asn	Cys
		195					200					205			
Ala	Arg	Ile	Ile	His	Gly	Asn	Gln	Ile	Ala	Thr	Asn	Gly	Val	Val	His
	210				215						220				
Val	Ile	Asp	Arg	Val	Leu	Thr	Gln	Ile	Gly	Thr	Ser	Ile	Gln	Asp	Phe
225					230					235					240
Ile	Glu	Ala	Glu	Asp	Asp	Leu	Ser	Ser	Phe	Arg	Ala	Ala	Ala	Ile	Thr
				245					250					255	
Ser	Asp	Ile	Leu	Glu	Ala	Leu	Gly	Arg	Asp	Gly	His	Phe	Thr	Leu	Phe
			260					265					270		
Ala	Pro	Thr	Asn	Glu	Ala	Phe	Glu	Lys	Leu	Pro	Arg	Gly	Val	Leu	Glu
		275					280					285			
Arg	Phe	Met	Gly	Asp	Lys	Val	Ala	Ser	Glu	Ala	Leu	Met	Lys	Tyr	His
	290				295						300				
Ile	Leu	Asn	Thr	Leu	Gln	Cys	Ser	Glu	Ser	Ile	Met	Gly	Gly	Ala	Val
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Phe	Glu	Thr	Leu	Glu	Gly	Asn	Thr	Ile	Glu	Ile	Gly	Cys	Asp	Gly	Asp
				325					330					335	
Ser	Ile	Thr	Val	Asn	Gly	Ile	Lys	Met	Val	Asn	Lys	Lys	Asp	Ile	Val
			340					345					350		
Thr	Asn	Asn	Gly	Val	Ile	His	Leu	Ile	Asp	Gln	Val	Leu	Ile	Pro	Asp
		355					360					365			
Ser	Ala	Lys	Gln	Val	Ile	Glu	Leu	Ala	Gly	Lys	Gln	Gln	Thr	Thr	Phe
	370				375						380				
Thr	Asp	Leu	Val	Ala	Gln	Leu	Gly	Leu	Ala	Ser	Ala	Leu	Arg	Pro	Asp
385					390					395					400
Gly	Glu	Tyr	Thr	Leu	Leu	Ala	Pro	Val	Asn	Asn	Ala	Phe	Ser	Asp	Asp
				405				410						415	
Thr	Leu	Ser	Met	Val	Gln	Arg	Leu	Leu	Lys	Leu	Ile	Leu	Gln	Asn	His
			420					425					430		
Ile	Leu	Lys	Val	Lys	Val	Gly	Leu	Asn	Glu	Leu	Tyr	Asn	Gly	Gln	Ile
		435					440					445			
Leu	Glu	Thr	Ile	Gly	Gly	Lys	Gln	Leu	Arg	Val	Phe	Val	Tyr	Arg	Thr
	450				455						460				
Ala	Val	Cys	Ile	Glu	Asn	Ser	Cys	Met	Glu	Lys	Gly	Ser	Lys	Gln	Gly
465					470					475					480
Arg	Asn	Gly	Ala	Ile	His	Ile	Phe	Arg	Glu	Ile	Ile	Lys	Pro	Ala	Glu
				485					490					495	
Lys	Ser	Leu	His	Glu	Lys	Leu	Lys	Gln	Asp	Lys	Arg	Phe	Ser	Thr	Phe
			500					505					510		
Leu	Ser	Leu	Leu	Glu	Ala	Ala	Asp	Leu	Lys	Glu	Leu	Leu	Thr	Gln	Pro
			515				520						525		
Gly	Asp	Trp	Thr	Leu	Phe	Val	Pro	Thr	Asn	Asp	Ala	Phe	Lys	Gly	Met
	530				535						540				
Thr	Ser	Glu	Glu	Lys	Glu	Ile	Leu	Ile	Arg	Asp	Lys	Asn	Ala	Leu	Gln
545					550					555					560
Asn	Ile	Ile	Leu	Tyr	His	Leu	Thr	Pro	Gly	Val	Phe	Ile	Gly	Lys	Gly
				565					570					575	
Phe	Glu	Pro	Gly	Val	Thr	Asn	Ile	Leu	Lys	Thr	Thr	Gln	Gly	Ser	Lys
			580				585						590		
Ile	Phe	Leu	Lys	Glu	Val	Asn	Asp	Thr	Leu	Leu	Val	Asn	Glu	Leu	Lys
		595					600					605			
Ser	Lys	Glu	Ser	Asp	Ile	Met	Thr	Thr	Asn	Gly	Val	Ile	His	Val	Val
	610					615					620				
Asp	Lys	Leu	Leu	Tyr	Pro	Ala	Asp	Thr	Pro	Val	Gly	Asn	Asp	Gln	Leu

625		630		635		640
Leu Glu Ile Leu Asn Lys Leu Ile Lys Tyr Ile Gln Ile Lys Phe Val						
		645		650		655
Arg Gly Ser Thr Phe Lys Glu Ile Pro Val Thr Val Tyr Lys Pro Ile						
		660		665		670
Ile Lys Lys Tyr Thr Lys Ile Ile Asp Gly Val Pro Val Glu Ile Thr						
		675		680		685
Glu Lys Glu Thr Arg Glu Glu Arg Ile Ile Thr Gly Pro Glu Ile Lys						
		690		695		700
Tyr Thr Arg Ile Ser Thr Gly Gly Gly Glu Thr Glu Glu Thr Leu Lys						
705		710		715		720
Lys Leu Leu Gln Glu Glu Val Thr Lys Val Thr Lys Phe Ile Glu Gly						
		725		730		735
Gly Asp Gly His Leu Phe Glu Asp Glu Glu Ile Lys Arg Leu Leu Gln						
		740		745		750
Gly Asp Thr Pro Val Arg Lys Leu Gln Ala Asn Lys Lys Val Gln Gly						
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Ser Arg Arg Arg Leu Arg Glu Gly Arg Ser Gln						
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<210> 181  
 <211> 2088  
 <212> DNA  
 <213> Homo sapiens

<400> 181

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ccactattta ataaaagtaa tagaatcaga aaaaaaaaaa aaaaaaaaaa 2088

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&lt;210&gt; 182

&lt;211&gt; 334

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 182

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 35          40          45
Gly His Arg Leu Thr Asp Arg Leu Gln Val Ala Ile Lys Val Ile Pro
 50          55          60
Arg Asn Arg Val Leu Gly Trp Ser Pro Leu Ser Asp Ser Val Thr Cys
 65          70          75          80
Pro Leu Glu Val Ala Leu Leu Trp Lys Val Gly Ala Gly Gly Gly His
          85          90          95
Pro Gly Val Ile Arg Leu Leu Asp Trp Phe Glu Thr Gln Glu Gly Phe
          100          105          110
Met Leu Val Leu Glu Arg Pro Leu Pro Ala Gln Asp Leu Phe Asp Tyr
          115          120          125
Ile Thr Glu Lys Gly Pro Leu Gly Glu Gly Pro Ser Arg Cys Phe Phe
          130          135          140
Gly Gln Val Val Ala Ala Ile Gln His Cys His Ser Arg Gly Val Val
          145          150          155          160
His Arg Asp Ile Lys Asp Glu Asn Ile Leu Ile Asp Leu Arg Arg Gly
          165          170          175
Cys Ala Lys Leu Ile Asp Phe Gly Ser Gly Ala Leu Leu His Asp Glu
          180          185          190
Pro Tyr Thr Asp Phe Asp Gly Thr Arg Val Tyr Ser Pro Pro Glu Trp
          195          200          205
Ile Ser Arg His Gln Tyr His Ala Leu Pro Ala Thr Val Trp Ser Leu
          210          215          220
Gly Ile Leu Leu Tyr Asp Met Val Cys Gly Asp Ile Pro Phe Glu Arg
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Asp Gln Glu Ile Leu Glu Ala Glu Leu His Phe Pro Ala His Val Ser
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Pro Asp Cys Cys Ala Leu Ile Arg Arg Cys Leu Ala Pro Lys Pro Ser
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Ser Arg Pro Ser Leu Glu Glu Ile Leu Leu Asp Pro Trp Met Gln Thr
          275          280          285
Pro Ala Glu Asp Val Thr Pro Gln Pro Leu Gln Arg Arg Pro Cys Pro
          290          295          300
Phe Gly Leu Val Leu Ala Thr Leu Ser Leu Ala Trp Pro Gly Leu Ala
          305          310          315          320
Pro Asn Gly Gln Lys Ser His Pro Met Ala Met Ser Gln Gly
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&lt;210&gt; 183

&lt;211&gt; 2304

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 183

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cattgccttg ctgaagatcc gttccaagga gggcaggtgt gcgcagccat cccggactat 960
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atcaataaaa tgtgattttt ctga 2304

```

&lt;210&gt; 184

&lt;211&gt; 431

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 184

```

Met Arg Ala Leu Leu Ala Arg Leu Leu Leu Cys Val Leu Val Val Ser
1          5          10          15
Asp Ser Lys Gly Ser Asn Glu Leu His Gln Val Pro Ser Asn Cys Asp
20          25          30
Cys Leu Asn Gly Gly Thr Cys Val Ser Asn Lys Tyr Phe Ser Asn Ile
35          40          45
His Trp Cys Asn Cys Pro Lys Lys Phe Gly Gly Gln His Cys Glu Ile
50          55          60
Asp Lys Ser Lys Thr Cys Tyr Glu Gly Asn Gly His Phe Tyr Arg Gly
65          70          75          80
Lys Ala Ser Thr Asp Thr Met Gly Arg Pro Cys Leu Pro Trp Asn Ser
85          90          95

```

Ala Thr Val Leu Gln Gln Thr Tyr His Ala His Arg Ser Asp Ala Leu  
 100 105 110  
 Gln Leu Gly Leu Gly Lys His Asn Tyr Cys Arg Asn Pro Asp Asn Arg  
 115 120 125  
 Arg Arg Pro Trp Cys Tyr Val Gln Val Gly Leu Lys Pro Leu Val Gln  
 130 135 140  
 Glu Cys Met Val His Asp Cys Ala Asp Gly Lys Lys Pro Ser Ser Pro  
 145 150 155 160  
 Pro Glu Glu Leu Lys Phe Gln Cys Gly Gln Lys Thr Leu Arg Pro Arg  
 165 170 175  
 Phe Lys Ile Ile Gly Gly Glu Phe Thr Thr Ile Glu Asn Gln Pro Trp  
 180 185 190  
 Phe Ala Ala Ile Tyr Arg Arg His Arg Gly Gly Ser Val Thr Tyr Val  
 195 200 205  
 Cys Gly Gly Ser Leu Ile Ser Pro Cys Trp Val Ile Ser Ala Thr His  
 210 215 220  
 Cys Phe Ile Asp Tyr Pro Lys Lys Glu Asp Tyr Ile Val Tyr Leu Gly  
 225 230 235 240  
 Arg Ser Arg Leu Asn Ser Asn Thr Gln Gly Glu Met Lys Phe Glu Val  
 245 250 255  
 Glu Asn Leu Ile Leu His Lys Asp Tyr Ser Ala Asp Thr Leu Ala His  
 260 265 270  
 His Asn Asp Ile Ala Leu Leu Lys Ile Arg Ser Lys Glu Gly Arg Cys  
 275 280 285  
 Ala Gln Pro Ser Arg Thr Ile Gln Thr Ile Cys Leu Pro Ser Met Tyr  
 290 295 300  
 Asn Asp Pro Gln Phe Gly Thr Ser Cys Glu Ile Thr Gly Phe Gly Lys  
 305 310 315 320  
 Glu Asn Ser Thr Asp Tyr Leu Tyr Pro Glu Gln Leu Lys Met Thr Val  
 325 330 335  
 Val Lys Leu Ile Ser His Arg Glu Cys Gln Gln Pro His Tyr Tyr Gly  
 340 345 350  
 Ser Glu Val Thr Thr Lys Met Leu Cys Ala Ala Asp Pro Gln Trp Lys  
 355 360 365  
 Thr Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Ser Leu  
 370 375 380  
 Gln Gly Arg Met Thr Leu Thr Gly Ile Val Ser Trp Gly Arg Gly Cys  
 385 390 395 400  
 Ala Leu Lys Asp Lys Pro Gly Val Tyr Thr Arg Val Ser His Phe Leu  
 405 410 415  
 Pro Trp Ile Arg Ser His Thr Lys Glu Asn Gly Leu Ala Leu  
 420 425 430

&lt;210&gt; 185

&lt;211&gt; 2123

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 185

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 gccgggggtcc ccggagttgc agctcccggg gctccggcgg cggctccacc ggcgaaagag 180  
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 gcgggcaaga ttgtgcctaa gtctctgctg ctcaagccgc accagaggga gaagatgtcc 360  
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 ttcgaggaca acgacttcgt gttcgtggtg ttggagctct gccgccggag gtctctcctg 480  
 gagccgcaca agaggaggaa agccctgact gagcctgagg cccgatacta cctacggcaa 540



```

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aaagtgcgaat atgacgggga gaggaagaag accctgtgtg ggactcctaa ttacatagct 720
cccgaggtgc tgagcaagaa agagcacagt ttcgaggtgg atgtgtggtc cattgggtgt 780
atcatgtata ccttgtagt gggcaaacca ctttttgaga cttcttgccct aaaagagacc 840
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ctcacagtcc tcaataaagg cttggagaac cccctgcctg agcgtccccg ggaaaaagaa 1140
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cgcgaaagtg atgagctcgc ccggctgccc tacctacgga cctggttccg caccgcgagc 1620
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gaattgtaca gaatatttct att 2123

```

&lt;210&gt; 186

&lt;211&gt; 603

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 186

```

Met Ser Ala Ala Val Thr Ala Gly Lys Leu Ala Arg Ala Pro Ala Asp
1          5          10          15
Pro Gly Lys Ala Gly Val Pro Gly Val Ala Ala Pro Gly Ala Pro Ala
20          25          30
Ala Ala Pro Pro Ala Lys Glu Ile Pro Glu Val Leu Val Asp Pro Arg
35          40          45
Ser Arg Arg Arg Tyr Val Arg Gly Arg Phe Leu Gly Lys Gly Gly Phe
50          55          60
Ala Lys Cys Phe Glu Ile Ser Asp Ala Asp Thr Lys Glu Val Phe Ala
65          70          75          80
Gly Lys Ile Val Pro Lys Ser Leu Leu Leu Lys Pro His Gln Arg Glu
85          90          95
Lys Met Ser Met Glu Ile Ser Ile His Arg Ser Leu Ala His Gln His
100          105          110
Val Val Gly Phe His Gly Phe Phe Glu Asp Asn Asp Phe Val Phe Val
115          120          125
Val Leu Glu Leu Cys Arg Arg Arg Ser Leu Leu Glu Pro His Lys Arg
130          135          140
Arg Lys Ala Leu Thr Glu Pro Glu Ala Arg Tyr Tyr Leu Arg Gln Ile
145          150          155          160
Val Leu Gly Cys Gln Tyr Leu His Arg Asn Arg Val Ile His Arg Asp
165          170          175
Leu Lys Leu Gly Asn Leu Phe Leu Asn Glu Asp Leu Glu Val Lys Ile
180          185          190
Gly Asp Phe Gly Leu Ala Thr Lys Val Glu Tyr Asp Gly Glu Arg Lys

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taagtctgtt cccttcaatt ctgtatcata cattgct 2617

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&lt;210&gt; 188

&lt;211&gt; 743

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 188

```

Met Ala Val Ala Val Arg Thr Leu Gln Glu Gln Leu Glu Lys Ala Lys
  1             5             10             15
Glu Ser Leu Lys Asn Val Asp Glu Asn Ile Arg Lys Leu Thr Gly Arg
      20             25             30
Asp Pro Asn Asp Val Arg Pro Ile Gln Ala Arg Leu Leu Ala Leu Ser
      35             40             45
Gly Pro Gly Gly Gly Arg Gly Arg Gly Ser Leu Leu Leu Arg Arg Gly
      50             55             60

```

Phe	Ser	Asp	Ser	Gly	Gly	Pro	Pro	Ala	Lys	Gln	Arg	Asp	Leu	Glu	Gly
65				70					75					80	
Ala	Val	Ser	Arg	Leu	Gly	Gly	Glu	Arg	Arg	Thr	Arg	Arg	Glu	Ser	Arg
			85					90					95		
Gln	Glu	Ser	Asp	Pro	Glu	Asp	Asp	Asp	Val	Lys	Lys	Pro	Ala	Leu	Gln
			100					105					110		
Ser	Ser	Val	Val	Ala	Thr	Ser	Lys	Glu	Arg	Thr	Arg	Arg	Asp	Leu	Ile
		115					120					125			
Gln	Asp	Gln	Asn	Met	Asp	Glu	Lys	Gly	Lys	Gln	Arg	Asn	Arg	Arg	Ile
	130					135				140					
Phe	Gly	Leu	Leu	Met	Gly	Thr	Leu	Gln	Lys	Phe	Lys	Gln	Glu	Ser	Thr
145					150					155					160
Val	Ala	Thr	Glu	Arg	Gln	Asn	Arg	Arg	Gln	Glu	Ile	Glu	Gln	Lys	Leu
				165					170					175	
Glu	Val	Gln	Ala	Glu	Glu	Glu	Arg	Lys	Gln	Val	Glu	Asn	Glu	Arg	Arg
			180					185					190		
Glu	Leu	Phe	Glu	Glu	Arg	Arg	Ala	Lys	Gln	Thr	Glu	Leu	Arg	Leu	Leu
		195					200					205			
Glu	Gln	Lys	Val	Glu	Leu	Ala	Gln	Leu	Gln	Glu	Glu	Trp	Asn	Glu	His
	210					215					220				
Asn	Ala	Lys	Ile	Ile	Lys	Tyr	Ile	Arg	Thr	Lys	Thr	Lys	Pro	His	Leu
225					230					235					240
Phe	Tyr	Ile	Pro	Gly	Arg	Met	Cys	Pro	Ala	Thr	Gln	Lys	Leu	Ile	Glu
				245					250					255	
Glu	Ser	Gln	Arg	Lys	Met	Asn	Ala	Leu	Phe	Asp	Gly	Arg	Arg	Ile	Glu
			260					265					270		
Phe	Ala	Glu	Gln	Ile	Asn	Lys	Met	Glu	Ala	Arg	Pro	Arg	Arg	Gln	Ser
		275					280					285			
Met	Lys	Glu	Lys	Glu	His	Gln	Val	Val	Arg	Asn	Glu	Glu	His	Lys	Ala
	290					295					300				
Glu	Gln	Glu	Glu	Gly	Lys	Val	Ala	Gln	Arg	Glu	Glu	Glu	Leu	Val	Glu
305				310						315					320
Thr	Gly	Asn	Gln	His	Asn	Asp	Val	Glu	Ile	Glu	Glu	Ala	Gly	Glu	Glu
				325					330					335	
Glu	Glu	Lys	Glu	Ile	Gly	Ile	Val	His	Ser	Asp	Ala	Glu	Lys	Glu	Gln
			340					345					350		
Glu	Glu	Glu	Glu	Gln	Lys	Gln	Glu	Met	Glu	Val	Lys	Met	Glu	Glu	Glu
		355					360					365			
Thr	Glu	Val	Arg	Glu	Ser	Glu	Lys	Gln	Gln	Asp	Ser	Gln	Pro	Glu	Glu
	370					375					380				
Val	Met	Asp	Val	Leu	Glu	Met	Val	Glu	Asn	Val	Lys	His	Val	Ile	Ala
385					390					395					400
Asp	Gln	Glu	Val	Met	Glu	Thr	Asn	Arg	Val	Glu	Ser	Val	Glu	Pro	Ser
				405					410					415	
Glu	Asn	Glu	Ala	Ser	Lys	Glu	Leu	Glu	Pro	Glu	Met	Glu	Phe	Glu	Ile
			420					425					430		
Glu	Pro	Asp	Lys	Glu	Cys	Lys	Ser	Leu	Ser	Pro	Gly	Lys	Glu	Asn	Val
	435						440					445			
Ser	Ala	Leu	Asp	Met	Glu	Lys	Glu	Ser	Asp	Glu	Lys	Glu	Glu	Lys	Glu
	450					455					460				
Ser	Glu	Pro	Gln	Pro	Glu	Pro	Val	Ala	Gln	Pro	Gln	Ala	Gln	Ser	Gln
465					470					475					480
Pro	Gln	Leu	Gln	Leu	Gln	Ser	Gln	Ser	Glu	Pro	Gln	Pro	Gln	Leu	Gln
				485					490					495	
Pro	Glu	Pro	Ala	Gln	Pro	Gln	Leu	Gln	Ser	Gln	Pro	Gln	Leu	Gln	Leu
			500					505					510		
Gln	Ser	Gln	Cys	His	Ala	Val	Leu	Gln	Ser	His	Pro	Pro	Ser	Gln	Pro
		515					520					525			
Glu	Asp	Leu	Ser	Leu	Ala	Val	Leu	Gln	Pro	Thr	Pro	Gln	Val	Thr	Gln

530		535		540
Glu His Gly His Phe Leu Pro Glu Arg Lys Asp Phe Pro Val Glu Ser				
545		550		560
Val Lys Leu Thr Glu Val Pro Val Asp Pro Val Leu Thr Val His Pro				
	565		570	575
Glu Ser Glu Ser Glu Thr Asn Thr Arg Ser Arg Ser Arg Gly Arg Thr				
	580		585	590
Arg Asn Arg Thr Thr Lys Ser Arg Ser Arg Ser Ser Ser Ser Ser				
	595		600	605
Ser Ser Ser Ser Ser Thr Ser Ser Ser Ser Gly Ser Ser Ser Ser				
	610		615	620
Gly Ser Ser Ser Ser Arg Ser Ser Ser Ser Ser Ser Ser Ser Thr Ser				
625		630		640
Gly Ser Ser Ser Arg Asp Ser Ser Ser Ser Thr Ser Ser Ser Ser Glu				
	645		650	655
Ser Arg Ser Arg Ser Arg Gly Arg Gly His Asn Arg Asp Arg Lys His				
	660		665	670
Arg Arg Ser Val Asp Arg Lys Arg Arg Asp Thr Ser Gly Leu Glu Arg				
	675		680	685
Ser His Lys Ser Ser Lys Gly Gly Ser Ser Arg Asp Thr Lys Gly Ser				
	690		695	700
Lys Asp Lys Asn Ser Arg Ser Asp Arg Lys Arg Ser Ile Ser Glu Ser				
705		710		720
Ser Arg Ser Gly Lys Arg Ser Ser Arg Ser Glu Arg Asp Arg Lys Ser				
	725		730	735
Asp Arg Lys Asp Lys Arg Arg				
740				

<210> 189  
 <211> 1182  
 <212> DNA  
 <213> Homo sapiens

<400> 189  
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 gccaggtaac aatgggtgcg ctgcaatcca gacagtaatt ctgcaaactg ccttgaagaa 180  
 aaaggaccaa tggtcgaact acttccagggt gaatccaaca agatcccccg tctgaggact 240  
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 tactctggat caggcttcgg ctccggctcc ggctctggat caggatctgg gagtggcttc 360  
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 tttaaacatc tgaaaaagaa gcttaagttt tatcatcctt ttttttctca tgaattctta 660  
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<210> 190  
 <211> 158  
 <212> PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 190

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Met Met Gln Lys Leu Leu Lys Cys Ser Arg Leu Val Leu Ala Leu Ala
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Leu Ile Leu Val Leu Glu Ser Ser Val Gln Gly Tyr Pro Thr Gln Arg
           20           25           30
Ala Arg Tyr Gln Trp Val Arg Cys Asn Pro Asp Ser Asn Ser Ala Asn
           35           40           45
Cys Leu Glu Glu Lys Gly Pro Met Phe Glu Leu Leu Pro Gly Glu Ser
 50           55           60
Asn Lys Ile Pro Arg Leu Arg Thr Asp Leu Phe Pro Lys Thr Arg Ile
 65           70           75           80
Gln Asp Leu Asn Arg Ile Phe Pro Leu Ser Glu Asp Tyr Ser Gly Ser
           85           90           95
Gly Phe Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Phe
           100          105          110
Leu Thr Glu Met Glu Gln Asp Tyr Gln Leu Val Asp Glu Ser Asp Ala
           115          120          125
Phe His Asp Asn Leu Arg Ser Leu Asp Arg Asn Leu Pro Ser Asp Ser
           130          135          140
Gln Asp Leu Gly Gln His Gly Leu Glu Glu Asp Phe Met Leu
145           150           155

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&lt;210&gt; 191

&lt;211&gt; 1595

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 191

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 <211> 175  
 <212> PRT  
 <213> Homo sapiens

<400> 192  
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 20 25 30  
 Arg Leu Lys Arg Ala Val Ser Glu His Gln Leu Leu His Asp Lys Gly  
 35 40 45  
 Lys Ser Ile Gln Asp Leu Arg Arg Phe Phe Leu His His Leu Ile  
 50 55 60  
 Ala Glu Ile His Thr Ala Glu Ile Arg Ala Thr Ser Glu Val Ser Pro  
 65 70 75 80  
 Asn Ser Lys Pro Ser Pro Asn Thr Lys Asn His Pro Val Arg Phe Gly  
 85 90 95  
 Ser Asp Asp Glu Gly Arg Tyr Leu Thr Gln Glu Thr Asn Lys Val Glu  
 100 105 110  
 Thr Tyr Lys Glu Gln Pro Leu Lys Thr Pro Gly Lys Lys Lys Gly  
 115 120 125  
 Lys Pro Gly Lys Arg Lys Glu Gln Glu Lys Lys Lys Arg Arg Thr Arg  
 130 135 140  
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 His Leu Ser Asp Thr Ser Thr Thr Ser Leu Glu Leu Asp Ser Arg  
 165 170 175

<210> 193  
 <211> 2657  
 <212> DNA  
 <213> Homo sapiens

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<400> 193  
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&lt;210&gt; 194

&lt;211&gt; 168

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 194

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20          25          30
Gly Lys Lys Glu Lys Pro Glu Lys Lys Val Lys Lys Ser Asp Cys Gly
35          40          45
Glu Trp Gln Trp Ser Val Cys Val Pro Thr Ser Gly Asp Cys Gly Leu
50          55          60
Gly Thr Arg Glu Gly Thr Arg Thr Gly Ala Glu Cys Lys Gln Thr Met
65          70          75          80
Lys Thr Gln Arg Cys Lys Ile Pro Cys Asn Trp Lys Lys Gln Phe Gly
85          90          95
Ala Glu Cys Lys Tyr Gln Phe Gln Ala Trp Gly Glu Cys Asp Leu Asn
100          105          110
Thr Ala Leu Lys Thr Arg Thr Gly Ser Leu Lys Arg Ala Leu His Asn
115          120          125
Ala Glu Cys Gln Lys Thr Val Thr Ile Ser Lys Pro Cys Gly Lys Leu
130          135          140
Thr Lys Pro Lys Pro Gln Ala Glu Ser Lys Lys Lys Lys Lys Glu Gly
145          150          155          160
Lys Lys Gln Glu Lys Met Leu Asp
165

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&lt;210&gt; 195



&lt;211&gt; 2972

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 195

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&lt;210&gt; 196

&lt;211&gt; 890

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 196

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Asp	Val	Val	Val	Ser	Pro	Met	Phe	Glu	Ser	Thr	Ala	Ala	Asp	Leu	Gly	20	25	30	
Ser	Val	Val	Arg	Lys	Asn	Leu	Leu	Ser	Asp	Cys	Ser	Val	Val	Ser	Thr	35	40	45	
Ser	Leu	Glu	Asp	Lys	Gln	Gln	Val	Pro	Ser	Glu	Asp	Ser	Met	Glu	Lys	50	55	60	
Val	Lys	Val	Tyr	Leu	Arg	Val	Arg	Pro	Leu	Leu	Pro	Ser	Glu	Leu	Glu	65	70	75	80
Arg	Gln	Glu	Asp	Gln	Gly	Cys	Val	Arg	Ile	Glu	Asn	Val	Glu	Thr	Leu	85	90	95	
Val	Leu	Gln	Ala	Pro	Lys	Asp	Ser	Phe	Ala	Leu	Lys	Ser	Asn	Glu	Arg	100	105	110	
Gly	Ile	Gly	Gln	Ala	Thr	His	Arg	Phe	Thr	Phe	Ser	Gln	Ile	Phe	Gly	115	120	125	
Pro	Glu	Val	Gly	Gln	Ala	Ser	Phe	Phe	Asn	Leu	Thr	Val	Lys	Glu	Met	130	135	140	
Val	Lys	Asp	Val	Leu	Lys	Gly	Gln	Asn	Trp	Leu	Ile	Tyr	Thr	Tyr	Gly	145	150	155	160
Val	Thr	Asn	Ser	Gly	Lys	Thr	His	Thr	Ile	Gln	Gly	Thr	Ile	Lys	Asp	165	170	175	
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Gly	Gln	Leu	His	Pro	Thr	Pro	Asp	Leu	Lys	Pro	Leu	Leu	Ser	Asn	Glu	195	200	205	
Val	Ile	Trp	Leu	Asp	Ser	Lys	Gln	Ile	Arg	Gln	Glu	Glu	Met	Lys	Lys	210	215	220	
Leu	Ser	Leu	Leu	Asn	Gly	Gly	Leu	Gln	Glu	Glu	Glu	Leu	Ser	Thr	Ser	225	230	235	240
Leu	Lys	Arg	Ser	Val	Tyr	Ile	Glu	Ser	Arg	Ile	Gly	Thr	Ser	Thr	Ser	245	250	255	
Phe	Asp	Ser	Gly	Ile	Ala	Gly	Leu	Ser	Ser	Ile	Ser	Gln	Cys	Thr	Ser	260	265	270	
Ser	Ser	Gln	Leu	Asp	Glu	Thr	Ser	His	Arg	Trp	Ala	Gln	Pro	Asp	Thr	275	280	285	
Ala	Pro	Leu	Pro	Val	Pro	Ala	Asn	Ile	Arg	Phe	Ser	Ile	Trp	Ile	Ser	290	295	300	
Phe	Phe	Glu	Ile	Tyr	Asn	Glu	Leu	Leu	Tyr	Asp	Leu	Leu	Glu	Pro	Pro	305	310	315	320
Ser	Gln	Gln	Arg	Lys	Arg	Gln	Thr	Leu	Arg	Leu	Cys	Glu	Asp	Gln	Asn	325	330	335	
Gly	Asn	Pro	Tyr	Val	Lys	Asp	Leu	Asn	Trp	Ile	His	Val	Gln	Asp	Ala	340	345	350	
Glu	Glu	Ala	Trp	Lys	Leu	Leu	Lys	Val	Gly	Arg	Lys	Asn	Gln	Ser	Phe	355	360	365	
Ala	Ser	Thr	His	Leu	Asn	Gln	Asn	Ser	Ser	Arg	Ser	His	Ser	Ile	Phe	370	375	380	
Ser	Ile	Arg	Ile	Leu	His	Leu	Gln	Gly	Glu	Gly	Asp	Ile	Val	Pro	Lys	385	390	395	400
Ile	Ser	Glu	Leu	Ser	Leu	Cys	Asp	Leu	Ala	Gly	Ser	Glu	Arg	Cys	Lys	405	410	415	
Asp	Gln	Lys	Ser	Gly	Glu	Arg	Leu	Lys	Glu	Ala	Gly	Asn	Ile	Asn	Thr	420	425	430	
Ser	Leu	His	Thr	Leu	Gly	Arg	Cys	Ile	Ala	Ala	Leu	Arg	Gln	Asn	Gln	435	440	445	

Gln	Asn	Arg	Ser	Lys	Gln	Asn	Leu	Val	Pro	Phe	Arg	Asp	Ser	Lys	Leu
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Thr	Arg	Val	Phe	Gln	Gly	Phe	Phe	Thr	Gly	Arg	Gly	Arg	Ser	Cys	Met
465					470					475					480
Ile	Val	Asn	Val	Asn	Pro	Cys	Ala	Ser	Thr	Tyr	Asp	Glu	Thr	Leu	His
				485					490					495	
Val	Ala	Lys	Phe	Ser	Ala	Ile	Ala	Ser	Gln	Leu	Val	His	Ala	Pro	Pro
				500				505					510		
Met	Gln	Leu	Gly	Phe	Pro	Ser	Leu	His	Ser	Phe	Ile	Lys	Glu	His	Ser
		515					520					525			
Leu	Gln	Val	Ser	Pro	Ser	Leu	Glu	Lys	Gly	Ala	Lys	Ala	Asp	Thr	Gly
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Leu	Asp	Asp	Asp	Ile	Glu	Asn	Glu	Ala	Asp	Ile	Ser	Met	Tyr	Gly	Lys
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Glu	Glu	Leu	Leu	Gln	Val	Val	Glu	Ala	Met	Lys	Thr	Leu	Leu	Leu	Lys
				565					570					575	
Glu	Arg	Gln	Glu	Lys	Leu	Gln	Leu	Glu	Met	His	Leu	Arg	Asp	Glu	Ile
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Cys	Asn	Glu	Met	Val	Glu	Gln	Met	Gln	Gln	Arg	Glu	Gln	Trp	Cys	Ser
	595						600					605			
Glu	His	Leu	Asp	Thr	Gln	Lys	Glu	Leu	Leu	Glu	Glu	Met	Tyr	Glu	Glu
	610					615					620				
Lys	Leu	Asn	Ile	Leu	Lys	Glu	Ser	Leu	Thr	Ser	Phe	Tyr	Gln	Glu	Glu
625					630					635					640
Ile	Gln	Glu	Arg	Asp	Glu	Lys	Ile	Glu	Glu	Leu	Glu	Ala	Leu	Leu	Gln
				645					650					655	
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				660				665					670		
Ala	Leu	Arg	Arg	Ser	Gln	Arg	Leu	Ala	Ala	Ser	Ala	Ser	Thr	Gln	Gln
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Leu	Gln	Glu	Val	Lys	Ala	Lys	Leu	Gln	Gln	Cys	Lys	Ala	Glu	Leu	Asn
	690					695					700				
Ser	Thr	Thr	Glu	Glu	Leu	His	Lys	Tyr	Gln	Lys	Met	Leu	Glu	Pro	Pro
705					710					715					720
Pro	Ser	Ala	Lys	Pro	Phe	Thr	Ile	Asp	Val	Asp	Lys	Lys	Leu	Glu	Glu
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Gly	Gln	Lys	Asn	Ile	Arg	Leu	Leu	Arg	Thr	Glu	Leu	Gln	Lys	Leu	Gly
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Glu	Ser	Leu	Gln	Ser	Ala	Glu	Arg	Ala	Cys	Cys	His	Ser	Thr	Gly	Ala
	755					760						765			
Gly	Lys	Leu	Arg	Gln	Ala	Leu	Thr	Thr	Cys	Asp	Asp	Ile	Leu	Ile	Lys
	770					775					780				
Gln	Asp	Gln	Thr	Leu	Ala	Glu	Leu	Gln	Asn	Asn	Met	Val	Leu	Val	Lys
785					790					795					800
Leu	Asp	Leu	Arg	Lys	Lys	Ala	Ala	Cys	Ile	Ala	Glu	Gln	Tyr	His	Thr
				805					810					815	
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Asn	Gln	Glu	Asn	Gln	Gln	Pro	Asn	Gln	Gln	Pro	Pro	Gly	Lys	Lys	Pro
				835			840					845			
Phe	Leu	Arg	Asn	Leu	Leu	Pro	Arg	Thr	Pro	Thr	Cys	Gln	Ser	Ser	Thr
	850					855					860				
Asp	Cys	Ser	Pro	Tyr	Ala	Arg	Ile	Leu	Arg	Ser	Arg	Arg	Ser	Pro	Leu
865					870					875					880
Leu	Lys	Ser	Gly	Pro	Phe	Gly	Lys	Lys	Tyr						
				885					890						

<211> 768  
 <212> DNA  
 <213> Homo sapiens

<400> 197  
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 gatggcttcg ccacaccaag agcccaaacc tggagacctg attgagattt tccgccttgg 120  
 ctatgagcac tgggcctgtg atataggaga tggctacgtg atccatctgg ctctccaag 180  
 tgagtacccc ggggctgggt cctccagtgt cttctcagtc ctgagcaaca gtgcagaggt 240  
 gaaacggggg cgcctggaag atgtggtggg aggctgttgc tatcgggtca acaacagctt 300  
 ggaccatgag taccaaccac ggcccgtgga ggtgatcatc agttctgcga aggagatggg 360  
 tggtcagaag atgaagtaca gtattgtgag caggaactgt gagcactttg tcgccagct 420  
 gagatatggc aagtcccgtg gtaaacaggt ggaaaaggcc aagggtgaag tcggtgtggc 480  
 cacggcgctt ggaatcctgg ttgttgctgg atgctctttt gcgattagga gatacaaaa 540  
 aaaagcaaca gcctgaagca gccacaaaat cctgtgttag aagcagctgt ggggggtcca 600  
 gtggagatga gcctcccca tgccctcagc agcctgacct tcgtgccctg tctcaggcgt 660  
 tctctagatc ctttcctctg tttccctctc tcgtggcaa aagtatgatc taattgaaac 720  
 aagactgaag gatcaataaa cagccatctg ccccttcaaa aaaaaaaa 768

<210> 198  
 <211> 164  
 <212> PRT  
 <213> Homo sapiens

<400> 198  
 Met Ala Ser Pro His Gln Glu Pro Lys Pro Gly Asp Leu Ile Glu Ile  
 1 5 10 15  
 Phe Arg Leu Gly Tyr Glu His Trp Ala Leu Tyr Ile Gly Asp Gly Tyr  
 20 25 30  
 Val Ile His Leu Ala Pro Pro Ser Glu Tyr Pro Gly Ala Gly Ser Ser  
 35 40 45  
 Ser Val Phe Ser Val Leu Ser Asn Ser Ala Glu Val Lys Arg Gly Arg  
 50 55 60  
 Leu Glu Asp Val Val Gly Gly Cys Cys Tyr Arg Val Asn Asn Ser Leu  
 65 70 75 80  
 Asp His Glu Tyr Gln Pro Arg Pro Val Glu Val Ile Ile Ser Ser Ala  
 85 90 95  
 Lys Glu Met Val Gly Gln Lys Met Lys Tyr Ser Ile Val Ser Arg Asn  
 100 105 110  
 Cys Glu His Phe Val Ala Gln Leu Arg Tyr Gly Lys Ser Arg Cys Lys  
 115 120 125  
 Gln Val Glu Lys Ala Lys Val Glu Val Gly Val Ala Thr Ala Leu Gly  
 130 135 140  
 Ile Leu Val Val Ala Gly Cys Ser Phe Ala Ile Arg Arg Tyr Gln Lys  
 145 150 155 160  
 Lys Ala Thr Ala

<210> 199  
 <211> 720  
 <212> DNA  
 <213> Homo sapiens

<400> 199  
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 gctgtcccgg cagtctccag ccgtcccgcc cgcttgtggc caaactggct ccagtcactc 120  
 ccgaaatgcc agtcgacttc actgggtact ggaagatgtt ggtcaacgag aatttcgagg 180  
 agtacctgcg cgccctcgac gtcaatgtgg ccttgcgcaa aatcgccaac ttgctgaagc 240

```

cagacaaaga gatcgtgcag gacggtgacc atatgatcat ccgcacgctg agcactttta 300
ggaactacat catggacttc caagttggga aggagtttga ggaggatctg acaggcatag 360
atgaccgcaa gtgcatgaca acagtgaact gggacggaga caagctccag tgtgtgcaga 420
agggtgagaa ggaggggctg ggctggaccc agtggatcga ggggtgatgag ctgcacctag 480
agatgagagt ggaaggtgtg gtctgcaagc aagtattcaa gaaggtgcag tgaggcccaa 540
gcagacaacc ttgtcccaac caatcagcag gatgtgtgag ccaggatccc tctttgcaca 600
gcatgaggca aaaatgtcca gccacccta ggcattctgt agcagagtct gtctcttggc 660
tttgtcactt ttccttttct taaaacaaa ccatgccaat aaagtgcact gtgttcaaaa 720

```

&lt;210&gt; 200

&lt;211&gt; 135

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 200

```

Met Pro Val Asp Phe Thr Gly Tyr Trp Lys Met Leu Val Asn Glu Asn
 1          5          10          15
Phe Glu Glu Tyr Leu Arg Ala Leu Asp Val Asn Val Ala Leu Arg Lys
      20          25          30
Ile Ala Asn Leu Leu Lys Pro Asp Lys Glu Ile Val Gln Asp Gly Asp
      35          40          45
His Met Ile Ile Arg Thr Leu Ser Thr Phe Arg Asn Tyr Ile Met Asp
      50          55          60
Phe Gln Val Gly Lys Glu Phe Glu Glu Asp Leu Thr Gly Ile Asp Asp
      65          70          75          80
Arg Lys Cys Met Thr Thr Val Ser Trp Asp Gly Asp Lys Leu Gln Cys
      85          90          95
Val Gln Lys Gly Glu Lys Glu Gly Arg Gly Trp Thr Gln Trp Ile Glu
      100          105          110
Gly Asp Glu Leu His Leu Glu Met Arg Val Glu Gly Val Val Cys Lys
      115          120          125
Gln Val Phe Lys Lys Val Gln
      130          135

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&lt;210&gt; 201

&lt;211&gt; 2383

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 201

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ggggtaccg cgcctttgct tcctggcgca cgcggagcct cctggagcct gccaccatcc 60
tgcctactac gtgctgccct gcgcccgcag ccatgtgcog caccctggcc gccttcccca 120
ccacctgcct ggagagagcc aaagagttca agacacgtct ggggatcttt cttcacaaat 180
cagagctggg ctgcgatact gggagtactg gcaagtcgga gtggggcagt aaacacagca 240
aagagaatag aaacttctca gaagatgtgc tgggggtggag agagtcgttc gacctgctgc 300
tgagcagtaa aaatggagtg gctgccttcc acgctttcct gaagacagag ttcagttagg 360
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tggcctccag ggcaaccagc atctttgagg agttcatttg cagttaggac cctaaagagg 480
tcaacattga ccatgagacc cgcgagctga cgaggatgaa cctgcagact gccacagcca 540
catgctttga tgcggtcagc gggaagacac gtaccctgat ggagaaggac tcctaccac 600
gcttcctgaa gtgcctgct taccgggacc tggtgcccga agcctcagcc gcctctgcca 660
ctctgtccag ctgcagcctg gacgagccct cacacacctg agtctccacg gcagttagga 720
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gcaggttctg caaagcaagt gcaagaggac aaaaaaaaaa aaaaaaaaaa aaaaatgagc 840
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ctctctgtgg ggcaaaaagg tggatatggg gtttagcact gctctcgttc tcaccggaga 1020

```

```

aggaagtgtt ctagtgttgt ttaggaaaca tgtggataaa gggaaccatg aaaatgagag 1080
gaggaaagac atccagatca gctgttttgc ctgttgctca gttgactctg attgcatcct 1140
gttttcctaa ttcccagact gttctgggca cggaaggagac cctggatgtg gagtcttccc 1200
ctttggccct cctcactggc ctctgggcta gccagagtc ccttagcttg tacctcgtaa 1260
cactcctgtg tgtctgtcca gccttgacgt catgtcaagg ccagcaagct gatgtgactc 1320
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tcttcctgga tgtgccctct ctgagttctg tgctgtctct tggaggcagg gccaggaga 1560
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tattttattat tgtaatttca gtttgcctct actggagaat ctcagcaggg gtttcagcct 2160
gactgtctcc ctttctctac cagactctac ctctgaatgt gctgggaacc tcttgagacc 2220
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ataaaaycaa aagtc aaata tgaaaaaaa aaaaaaaaaa aaa 2383

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&lt;210&gt; 202

&lt;211&gt; 202

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 202

```

Met Cys Arg Thr Leu Ala Ala Phe Pro Thr Thr Cys Leu Glu Arg Ala
 1          5          10          15
Lys Glu Phe Lys Thr Arg Leu Gly Ile Phe Leu His Lys Ser Glu Leu
 20          25          30
Gly Cys Asp Thr Gly Ser Thr Gly Lys Ser Glu Trp Gly Ser Lys His
 35          40          45
Ser Lys Glu Asn Arg Asn Phe Ser Glu Asp Val Leu Gly Trp Arg Glu
 50          55          60
Ser Phe Asp Leu Leu Leu Ser Ser Lys Asn Gly Val Ala Ala Phe His
 65          70          75          80
Ala Phe Leu Lys Thr Glu Phe Ser Glu Glu Asn Leu Glu Phe Trp Leu
 85          90          95
Ala Cys Glu Glu Phe Lys Lys Ile Arg Ser Ala Thr Lys Leu Ala Ser
100          105          110
Arg Ala His Gln Ile Phe Glu Glu Phe Ile Cys Ser Glu Ala Pro Lys
115          120          125
Glu Val Asn Ile Asp His Glu Thr Arg Glu Leu Thr Arg Met Asn Leu
130          135          140
Gln Thr Ala Thr Ala Thr Cys Phe Asp Ala Ala Gln Gly Lys Thr Arg
145          150          155          160
Thr Leu Met Glu Lys Asp Ser Tyr Pro Arg Phe Leu Lys Ser Pro Ala
165          170          175
Tyr Arg Asp Leu Ala Ala Gln Ala Ser Ala Ala Ser Ala Thr Leu Ser
180          185          190
Ser Cys Ser Leu Asp Glu Pro Ser His Thr
195          200

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&lt;210&gt; 203

<211> 616  
 <212> DNA  
 <213> Homo sapiens

<400> 203  
 ctcccctggg agcctggtgc ccttgccttc cttcctgggt ctgtctctgc cacctgggtct 60  
 gccacagatc catgatgtgc agttctcttg agcaggcgct ggctgtgctg gtcactacct 120  
 tccacaagta ctctgcca gagggcgaca agttcaagct gagtaagggg gaaatgaagg 180  
 aacttctgca caaggagctg cccagctttg tggggcattc cagagaacca tgtgctgtga 240  
 gggccttccg agtccatctg tttaatcctg tcattggaga cttgagaaac cagagcccag 300  
 aagggaaaag tgattgtccc aagatcacac agcactggag aaagtggatg aggaggggct 360  
 gaagaagctg atgggcagcc tggatgagaa cagtgaccag cagggtgact tccaggagta 420  
 tgctgttttc ctggcactca tctactgtcat gtgcaatgac ttcttccagg gctgcccaga 480  
 ccgaccctga agcagaactc ttgacttcct gcctatggatc tcttggggcc aggactgttg 540  
 atgcctttga gttttgtatt caataaactt tttttgtctg ttgaaaaaaa aaaaaaaaaa 600  
 aaaaaaaaaa aaaaaa 616

<210> 204  
 <211> 96  
 <212> PRT  
 <213> Homo sapiens

<400> 204  
 Met Met Cys Ser Ser Leu Glu Gln Ala Leu Ala Val Leu Val Thr Thr  
 1 5 10 15  
 Phe His Lys Tyr Ser Cys Gln Glu Gly Asp Lys Phe Lys Leu Ser Lys  
 20 25 30  
 Gly Glu Met Lys Glu Leu Leu His Lys Glu Leu Pro Ser Phe Val Gly  
 35 40 45  
 His Ser Arg Glu Pro Cys Ala Val Arg Ala Phe Arg Val His Leu Phe  
 50 55 60  
 Asn Pro Val Ile Gly Asp Leu Arg Asn Gln Ser Pro Glu Gly Lys Ser  
 65 70 75 80  
 Asp Cys Pro Lys Ile Thr Gln His Trp Arg Lys Trp Met Arg Arg Gly  
 85 90 95

<210> 205  
 <211> 428  
 <212> DNA  
 <213> Homo sapiens

<400> 205  
 ctgggtctgt ctctgccacc tggctctgcca cagatccatg atgtgcagtt ctctggagca 60  
 ggcgctggct gtgctgggtca ctaccttcca caagtactcc tgccaagagg gcgacaagtt 120  
 caagctgagt aagggggaaa tgaaggaact tctgcacaag gagctgcccc gctttgtggg 180  
 ggagaaaagt gatgaggagg ggctgaagaa gctgatgggc agcctggatg agaacagtga 240  
 ccagcaggtg gacttccagg agtatgctgt tttcctggca ctcactactg tcatgtgcaa 300  
 tgactttctc cagggtgcc cagaccgacc ctgaagcaga actcttgact tcctgccatg 360  
 gatctcttgg gccaggact gttgatgcct ttgagttttg tattcaataa actttttttg 420  
 tctgttga 428

<210> 206  
 <211> 97  
 <212> PRT  
 <213> Homo sapiens

<400> 206  
 Met Cys Ser Ser Leu Glu Gln Ala Leu Ala Val Leu Val Thr Thr Phe

270

1	5	10	15
His Lys Tyr Ser Cys Gln Glu Gly Asp Lys Phe Lys Leu Ser Lys Gly			
	20	25	30
Glu Met Lys Glu Leu Leu His Lys Glu Leu Pro Ser Phe Val Gly Glu			
	35	40	45
Lys Val Asp Glu Glu Gly Leu Lys Lys Leu Met Gly Ser Leu Asp Glu			
	50	55	60
Asn Ser Asp Gln Gln Val Asp Phe Gln Glu Tyr Ala Val Phe Leu Ala			
65	70	75	80
Leu Ile Thr Val Met Cys Asn Asp Phe Phe Gln Gly Cys Pro Asp Arg			
	85	90	95
Pro			

&lt;210&gt; 207

&lt;211&gt; 799

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 207

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cactcccaaa gaactgggta ctcaacactg agcagatctg ttctttgagc taaaaaccat 60
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cggcgaatca gaagcagcaa gcaactttga ctgctgtctt ggatacacag accgtattct 180
tcatacctaaa tttattgtgg gcttcacacg gcagctggcc aatgaaggct gtgacatcaa 240
tgctatcatc tttcacacaa agaaaaagt gtctgtgtgc gcaaatacaa aacagacttg 300
ggtgaaatat attgtgctgc tcctcagtaa aaaagtcaag aacatgtaaa aactgtggct 360
tttctggaat ggaattggac atagcccaag aacagaaaga accttgctgg ggttggaggt. 420
ttcacttgca catcatggag ggtttagtgc ttatctaatt tgtgcctcac tggacttgtc 480
caattaatga agttgattca tattgcatca tagtttgctt tgtttaagca tcacattaaa 540
gttaaaactgt attttatgtt atttatagct gtaggttttc tgtgttttagc tatttaatac 600
taattttcca taagctatatt tggtttagtg caaagtataa aattatatatt gggggggaat 660
aagattatat ggactttctt gcaagcaaca agctattttt taaaaaaact atttaacatt 720
cttttgttta tattgttttg tctcctaaat tgttgtaatt gcattataaa ataagaaaaa 780
cattaataag acaaatatt

```

&lt;210&gt; 208

&lt;211&gt; 96

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 208

Met Cys Cys Thr Lys Ser Leu Leu Leu Ala Ala Leu Met Ser Val Leu	
1	5
Leu Leu His Leu Cys Gly Glu Ser Glu Ala Ala Ser Asn Phe Asp Cys	
	20
Cys Leu Gly Tyr Thr Asp Arg Ile Leu His Pro Lys Phe Ile Val Gly	
	35
Phe Thr Arg Gln Leu Ala Asn Glu Gly Cys Asp Ile Asn Ala Ile Ile	
	50
Phe His Thr Lys Lys Lys Leu Ser Val Cys Ala Asn Pro Lys Gln Thr	
65	70
Trp Val Lys Tyr Ile Val Arg Leu Leu Ser Lys Lys Val Lys Asn Met	
	85
	90
	95

&lt;210&gt; 209

&lt;211&gt; 2133

&lt;212&gt; DNA



&lt;213&gt; Homo sapiens

&lt;400&gt; 209

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agggcctgga tcttctttct cttttgcttg gccgggaggg ccttggcagc ccctcagcaa 120
gaagccctgc ctgatgagac agaggtggtg gaagaaactg tggcagaggt gactgaggta 180
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aatgagaagc gcctggaggc aggagaccac cccgtggagc tgctggcccc ggacttcgag 720
aagaactata acatgtacat cttccctgta cactggcagt tcggccagct ggaccagcac 780
ccattgacg ggtacctctc ccacaccgag ctggctccac tgcgtgctcc cctcatcccc 840
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ctgaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaa 2133

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&lt;210&gt; 210

&lt;211&gt; 303

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 210

```

Met Arg Ala Trp Ile Phe Phe Leu Leu Cys Leu Ala Gly Arg Ala Leu
1      5      10      15
Ala Ala Pro Gln Glu Ala Leu Pro Asp Glu Thr Glu Val Val Glu
20      25      30
Glu Thr Val Ala Glu Val Thr Glu Val Ser Val Gly Ala Asn Pro Val
35      40      45
Gln Val Glu Val Gly Glu Phe Asp Asp Gly Ala Glu Glu Thr Glu Glu
50      55      60
Glu Val Val Ala Glu Asn Pro Cys Gln Asn His His Cys Lys His Gly
65      70      75      80
Lys Val Cys Glu Leu Asp Glu Asn Asn Thr Pro Met Cys Val Cys Gln
85      90      95
Asp Pro Thr Ser Cys Pro Ala Pro Ile Gly Glu Phe Glu Lys Val Cys

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100					105					110						
Ser	Asn	Asp	Asn	Lys	Thr	Phe	Asp	Ser	Ser	Cys	His	Phe	Phe	Ala	Thr	
115					120					125						
Lys	Cys	Thr	Leu	Glu	Gly	Thr	Lys	Lys	Gly	His	Lys	Leu	His	Leu	Asp	
130					135					140						
Tyr	Ile	Gly	Pro	Cys	Lys	Tyr	Ile	Pro	Pro	Cys	Leu	Asp	Ser	Glu	Leu	
145					150					155					160	
Thr	Glu	Phe	Pro	Leu	Arg	Met	Arg	Asp	Trp	Leu	Lys	Asn	Val	Leu	Val	
165					170					175						
Thr	Leu	Tyr	Glu	Arg	Asp	Glu	Asp	Asn	Asn	Leu	Leu	Thr	Glu	Lys	Gln	
180					185					190						
Lys	Leu	Arg	Val	Lys	Lys	Ile	His	Glu	Asn	Glu	Lys	Arg	Leu	Glu	Ala	
195					200					205						
Gly	Asp	His	Pro	Val	Glu	Leu	Leu	Ala	Arg	Asp	Phe	Glu	Lys	Asn	Tyr	
210					215					220						
Asn	Met	Tyr	Ile	Phe	Pro	Val	His	Trp	Gln	Phe	Gly	Gln	Leu	Asp	Gln	
225					230					235					240	
His	Pro	Ile	Asp	Gly	Tyr	Leu	Ser	His	Thr	Glu	Leu	Ala	Pro	Leu	Arg	
245					250					255						
Ala	Pro	Leu	Ile	Pro	Met	Glu	His	Cys	Thr	Thr	Arg	Phe	Phe	Glu	Thr	
260					265					270						
Cys	Asp	Leu	Asp	Asn	Asp	Lys	Tyr	Ile	Ala	Leu	Asp	Glu	Trp	Ala	Gly	
275					280					285						
Cys	Phe	Gly	Ile	Lys	Gln	Lys	Asp	Ile	Asp	Lys	Asp	Leu	Val	Ile		
290					295					300						

&lt;210&gt; 211

&lt;211&gt; 2228

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens.

&lt;400&gt; 211

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ggtacagtca tcacaagcct gttcggcggg actgtgatgg ccagagagat gacgatctta 60
ggatcggctg ttttgactct cctgttggcc ggctatttgg cacaacagta tttaccattg 120
cctactccta aagtgattgg tattgatctt ggcaccacct attgttctgt tgggggtgtt 180
tttcctggca caggaaaagt aaagggtgatt ccagatgaaa atgggcatat cagcatatcc 240
agcatgggtg cttttactga caatgatgta tatgtgggat atgaaagcgt agagctggca 300
gattcaaatc ctcaaaacac aatatatgat gccaaaagat tcataggcaa gatttttacc 360
gcagaagagt tggaggctga aattggcaga taccatttta aggtttttaa caaaaatgga 420
atggttgagt tttctgtgac aagtaatgag accatcacag tgtccccaga atatgttggc 480
tctcgactat tgttgaagt aaaggaaatg gcagaggcat atcttggaaat gccagttgcc 540
aatgctgtca tttctgtacc agcagaattt gatctaaaac agagaaattc aacaattgaa 600
gctgctaacc ttgcaggact gaagattttg aggttaataa atgaaccac agcagcagct 660
atggcctatg gtctccacaa ggctgacgtc ttccacgtct tggatgata cttgggcgga 720
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tctggaaaca ataaacttgg aggacaggac ttcaatcaga gattgcttca gtacttatat 840
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agacaagctg tggaaatggg caaattaaat ctgactcttc atcaatctgc tcagttgtca 960
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ctttctgata agaaaagtgg agaaagtcag gttttatttg aaacagaaat atcacggaaa 1140
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ttgaaagaag gccacctgga aaagactgag attgatgagg tgggttttagt tgggggctcc 1260
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aacttcaact gaattctgca gaaataatgg ttatttgtga acttgtctga tgatctcttc 1500
ccatttatca gattacctt tccacaaaag aaagtctcta aaatatcaca gatttaccta 1560

```

```

gagggcaaca tttagatata ggaaaatttt acatagtgtt ttgtcttagg attagacgtg 1620
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gattcccagt tcttactaaa ttgtattagc aggagctggg aattacttgt attatcacat 1860
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aaatgtttca gcacatata atagaaatag ccaattatat tctagtctct ttatgtcctg 2160
tacatcattc tctgcttggg tttccattat tctgtttggg tagagaataa aattggtaat 2220
tgcatttg                                     2228

```

&lt;210&gt; 212

&lt;211&gt; 471

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 212

```

Met Ala Arg Glu Met Thr Ile Leu Gly Ser Ala Val Leu Thr Leu Leu
1      5      10      15
Leu Ala Gly Tyr Leu Ala Gln Gln Tyr Leu Pro Leu Pro Thr Pro Lys
20     25     30
Val Ile Gly Ile Asp Leu Gly Thr Thr Tyr Cys Ser Val Gly Val Phe
35     40     45
Phe Pro Gly Thr Gly Lys Val Lys Val Ile Pro Asp Glu Asn Gly His
50     55     60
Ile Ser Ile Pro Ser Met Val Ser Phe Thr Asp Asn Asp Val Tyr Val
65     70     75     80
Gly Tyr Glu Ser Val Glu Leu Ala Asp Ser Asn Pro Gln Asn Thr Ile
85     90     95
Tyr Asp Ala Lys Arg Phe Ile Gly Lys Ile Phe Thr Ala Glu Glu Leu
100    105    110
Glu Ala Glu Ile Gly Arg Tyr Pro Phe Lys Val Leu Asn Lys Asn Gly
115    120    125
Met Val Glu Phe Ser Val Thr Ser Asn Glu Thr Ile Thr Val Ser Pro
130    135    140
Glu Tyr Val Gly Ser Arg Leu Leu Leu Lys Leu Lys Glu Met Ala Glu
145    150    155    160
Ala Tyr Leu Gly Met Pro Val Ala Asn Ala Val Ile Ser Val Pro Ala
165    170    175
Glu Phe Asp Leu Lys Gln Arg Asn Ser Thr Ile Glu Ala Ala Asn Leu
180    185    190
Ala Gly Leu Lys Ile Leu Arg Val Ile Asn Glu Pro Thr Ala Ala Ala
195    200    205
Met Ala Tyr Gly Leu His Lys Ala Asp Val Phe His Val Leu Val Ile
210    215    220
Asp Leu Gly Gly Gly Thr Leu Asp Val Ser Leu Leu Asn Lys Gln Gly
225    230    235    240
Gly Met Phe Leu Thr Arg Ala Met Ser Gly Asn Asn Lys Leu Gly Gly
245    250    255
Gln Asp Phe Asn Gln Arg Leu Leu Gln Tyr Leu Tyr Lys Gln Ile Tyr
260    265    270
Gln Thr Tyr Gly Phe Val Pro Ser Arg Lys Glu Glu Ile His Arg Leu
275    280    285
Arg Gln Ala Val Glu Met Val Lys Leu Asn Leu Thr Leu His Gln Ser
290    295    300
Ala Gln Leu Ser Val Leu Leu Thr Val Glu Glu Gln Asp Arg Lys Glu
305    310    315    320

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```
<210> 213
<211> 1224
<212> DNA
<213> Homo sapiens
```

<400> 213						
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gccagaaagg	agaactccta	cccctggccc	tacggccgac	agacggctcc	atctggcctg	120
agcaccctgc	cccagcgagt	cctccggaaa	gagcctgtca	ccccactgtc	acttgtcctc	180
atgagccgct	ccaatgtcca	gcccacagct	gccctggcc	agaagtgat	ggayaatagc	240
atggggacac	ccgacatctt	aacgcggcac	ttcacaattg	atgacttga	gattggcgt	300
cctctgggca	aaggcaagtt	tggaaacgtg	tacttggtc	gggagaagaa	aagccatttc	360
atcgtggcg	tcaaggtcct	cttcaagtcc	cagatagaga	aggagggcgt	ggagcatcag	420
ctgcgacag	agatcgaaat	ccaggcccac	ctgcaccatc	ccaacatcct	gcgtctctac	480
aactattttt	atgacgggag	gaggatctac	ttgatcttag	agtatgccc	cccgggggag	540
cttacaagg	agctgcagaa	gagctgcaca	tttgacgagc	agcgaacagc	cagcatcatg	600
gaggagttgg	cagatgctct	aatgtactgc	catgggaaga	aggtgattca	cagagacata	660
aagccagaaa	atctgctctt	agggctcaag	ggagagctga	agattgctga	cttcggctgg	720
tctgtgcatg	cgccctccct	gaggaggaag	acaatgtgtg	gcaccttga	ctacctgccc	780
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tctgtgcct	gatggtccct	gtcattcact	cgggtgcgtg	tgtttgatat	tctgtgtatg	1140
tataggggaa	agaagggatc	cctaactgtt	cccttatctg	ttttctacct	cctcctttgt	1200
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```
<210> 214
<211> 344
<212> PRT
<213> Homo sapiens
```

```

<400> 214
Met Ala Gln Lys Glu Asn Ser Tyr Pro Trp Pro Tyr Gly Arg Gln Thr
 1          5          10          15
Ala Pro Ser Gly Leu Ser Thr Leu Pro Gln Arg Val Leu Arg Lys Glu

```

```
<210> 215
<211> 1421
<212> DNA
<213> Homo sapiens
```

<400> 215							
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cagtgattc	tcgggccgat	gttctcagga	aaaagcacag	agttgatgag	acgcgtccgt	180	
cgcttccaga	ttgctcagta	caagtgcctg	gtgatcaagt	atgccaaaga	cactcgctac	240	
agcagcagct	tctgcacaca	tgaccggaac	accatggagg	cgctgcccgc	ctgcctgctc	300	
cgagacgtgg	cccaggaggc	cctgggcgtg	gctgtcatag	gcacgcagca	ggggcagttt	360	
ttccctgaca	tcatggagtt	ctgcgaggcc	atggccaacg	ccgggaagac	cgtaattgtg	420	
ctgcactcgg	atgggacctt	ccagaggaag	ccatttgggg	ccatcctgaa	cctgggtgcg	480	
gtggccgaga	gcgtggtgaa	gctgacggcg	gtgtgcatgg	agtgtctccg	ccgaagccgc	540	
tataccaaga	ggctcggcac	agagaaggag	gtcgagggtga	ttggggggagc	agacaagtac	600	

```

cactccgtgt gtcggctctg ctacttcaag aaggcctcag gccagcctgc cgggccggac 660
aacaagaga actgcccagt gccaggaaag ccagggggaag ccgtggctgc caggaagctc 720
tttgcacac agcagattct gcaatgcagc cctgccaaact gagggacctg caagggccgc 780
ccgctccctt cctgccactg ccgcctactg gacgctgccc tgcattgctgc ccagccactc 840
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tgtgtggctg cccacactgc cgcattgctcc ctctctcct acccactggg ctgcttaaag 960
cttccctctc agctgctggg acgatcgccc aggctggagc tggccccgct tgggtggcctg 1020
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&lt;210&gt; 216

&lt;211&gt; 234

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 216

```

Met Ser Cys Ile Asn Leu Pro Thr Val Leu Pro Gly Ser Pro Ser Lys
1           5           10           15
Thr Arg Gly Gln Ile Gln Val Ile Leu Gly Pro Met Phe Ser Gly Lys
20           25           30
Ser Thr Glu Leu Met Arg Arg Val Arg Arg Phe Gln Ile Ala Gln Tyr
35           40           45
Lys Cys Leu Val Ile Lys Tyr Ala Lys Asp Thr Arg Tyr Ser Ser Ser
50           55           60
Phe Cys Thr His Asp Arg Asn Thr Met Glu Ala Leu Pro Ala Cys Leu
65           70           75           80
Leu Arg Asp Val Ala Gln Glu Ala Leu Gly Val Ala Val Ile Gly Ile
85           90           95
Asp Glu Gly Gln Phe Phe Pro Asp Ile Met Glu Phe Cys Glu Ala Met
100          105          110
Ala Asn Ala Gly Lys Thr Val Ile Val Ala Ala Leu Asp Gly Thr Phe
115          120          125
Gln Arg Lys Pro Phe Gly Ala Ile Leu Asn Leu Val Pro Leu Ala Glu
130          135          140
Ser Val Val Lys Leu Thr Ala Val Cys Met Glu Cys Phe Arg Glu Ala
145          150          155          160
Ala Tyr Thr Lys Arg Leu Gly Thr Glu Lys Glu Val Glu Val Ile Gly
165          170          175
Gly Ala Asp Lys Tyr His Ser Val Cys Arg Leu Cys Tyr Phe Lys Lys
180          185          190
Ala Ser Gly Gln Pro Ala Gly Pro Asp Asn Lys Glu Asn Cys Pro Val
195          200          205
Pro Gly Lys Pro Gly Glu Ala Val Ala Ala Arg Lys Leu Phe Ala Pro
210          215          220
Gln Gln Ile Leu Gln Cys Ser Pro Ala Asn
225          230

```

&lt;210&gt; 217

&lt;211&gt; 2307

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

<221> misc\_feature

<222> 1691, 1698, 1705, 1708, 1709, 1713, 1717, 1720, 1724, 1728,  
1733, 1741, 1746, 1748, 1755, 1770, 1774, 1791, 1802, 1821,  
1838, 1856, 1859, 1864, 1908, 1959, 1997, 2012, 2038, 2143

<223> n = A,T,C or G

<400> 217

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cctgccctgc actcgggcct cctccagcca gtgctgacca gggacttctg acctgctggc 180
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gctacaggga gaccgggagg atcacagagc cagcatgtta caggatcctg acagtgatca 300
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cagaaagggtg gggatcccca tcatcatagc actactgagc ctggcgagta tcatcattgt 420
ggttgtcctc atcaagggtga ttctggataa atactacttc ctctgcgggc agcctctcca 480
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ggagcactgt gtcaagagct tcccgaagg gcctgcagtg gcagtcgcc tctccaagga 600
ccgatccaca ctgcagggtgc tggactcggc cacagggaac tggttctctg cctgtttcga 660
caacttcaca gaagctctcg ctgagacagc ctgtaggcag atgggctaca gcagcaaacc 720
cactttcaga gctgtggaga ttggcccaga ccaggatctg gatgttggtg aaatcacaga 780
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gccnactga acaaggctctc aggggtattg ctaagccaag aaggaacntt tcccacacta 1920
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gaaagggctc gcgccangcc ctgtccgtct tncaccatc cccaagccta ctagagcnaa 2040
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aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa ataaataaaa aaaaactcga gggggggccc 2220
ggtacccaat tcgccctata gtgagtcgta ttacaattca ctggccgtcg ttttacaacg 2280
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<210> 218

<211> 428

<212> PRT

<213> Homo sapiens

<400> 218

```

Met Leu Gln Asp Pro Asp Ser Asp Gln Pro Leu Asn Ser Leu Asp Val
 1             5             10             15
Lys Pro Leu Arg Lys Pro Arg Ile Pro Met Glu Thr Phe Arg Lys Val
          20          25          30
Gly Ile Pro Ile Ile Ile Ala Leu Leu Ser Leu Ala Ser Ile Ile Ile
      35              40              45

```

Val	Val	Val	Leu	Ile	Lys	Val	Ile	Leu	Asp	Lys	Tyr	Tyr	Phe	Leu	Cys
50						55					60				
Gly	Gln	Pro	Leu	His	Phe	Ile	Pro	Arg	Lys	Gln	Leu	Cys	Asp	Gly	Glu
65					70					75					80
Leu	Asp	Cys	Pro	Leu	Gly	Glu	Asp	Glu	Glu	His	Cys	Val	Lys	Ser	Phe
				85					90					95	
Pro	Glu	Gly	Pro	Ala	Val	Ala	Val	Arg	Leu	Ser	Lys	Asp	Arg	Ser	Thr
			100					105					110		
Leu	Gln	Val	Leu	Asp	Ser	Ala	Thr	Gly	Asn	Trp	Phe	Ser	Ala	Cys	Phe
		115					120					125			
Asp	Asn	Phe	Thr	Glu	Ala	Leu	Ala	Glu	Thr	Ala	Cys	Arg	Gln	Met	Gly
	130					135					140				
Tyr	Ser	Ser	Lys	Pro	Thr	Phe	Arg	Ala	Val	Glu	Ile	Gly	Pro	Asp	Gln
145					150					155					160
Asp	Leu	Asp	Val	Val	Glu	Ile	Thr	Glu	Asn	Ser	Gln	Glu	Leu	Arg	Met
				165					170					175	
Arg	Asn	Ser	Ser	Gly	Pro	Cys	Leu	Ser	Gly	Ser	Leu	Val	Ser	Leu	His
			180					185					190		
Cys	Leu	Ala	Cys	Gly	Lys	Ser	Leu	Lys	Thr	Pro	Arg	Val	Val	Gly	Gly
		195					200					205			
Glu	Glu	Ala	Ser	Val	Asp	Ser	Trp	Pro	Trp	Gln	Val	Ser	Ile	Gln	Tyr
	210					215					220				
Asp	Lys	Gln	His	Val	Cys	Gly	Gly	Ser	Ile	Leu	Asp	Pro	His	Trp	Val
225					230					235					240
Leu	Thr	Ala	Ala	His	Cys	Phe	Arg	Lys	His	Thr	Asp	Val	Phe	Asn	Trp
				245					250					255	
Lys	Val	Arg	Ala	Gly	Ser	Asp	Lys	Leu	Gly	Ser	Phe	Pro	Ser	Leu	Ala
			260					265					270		
Val	Ala	Lys	Ile	Ile	Ile	Ile	Glu	Phe	Asn	Pro	Met	Tyr	Pro	Lys	Asp
		275					280					285			
Asn	Asp	Ile	Ala	Leu	Met	Lys	Leu	Gln	Phe	Pro	Leu	Thr	Phe	Ser	Gly
	290					295					300				
Thr	Val	Arg	Pro	Ile	Cys	Leu	Pro	Phe	Phe	Asp	Glu	Glu	Leu	Thr	Pro
305					310					315					320
Ala	Thr	Pro	Leu	Trp	Ile	Ile	Gly	Trp	Gly	Phe	Thr	Lys	Gln	Asn	Gly
				325					330					335	
Gly	Lys	Met	Ser	Asp	Ile	Leu	Leu	Gln	Ala	Ser	Val	Gln	Val	Ile	Asp
			340					345					350		
Ser	Thr	Arg	Cys	Asn	Ala	Asp	Asp	Ala	Tyr	Gln	Gly	Glu	Val	Thr	Glu
		355				360						365			
Lys	Met	Met	Cys	Ala	Gly	Ile	Pro	Glu	Gly	Gly	Val	Asp	Thr	Cys	Gln
	370					375					380				
Gly	Asp	Ser	Gly	Gly	Pro	Leu	Met	Tyr	Gln	Ser	Asp	Gln	Trp	His	Val
385					390					395					400
Val	Gly	Ile	Val	Ser	Trp	Gly	Tyr	Gly	Cys	Gly	Gly	Pro	Ser	Thr	Pro
				405					410					415	
Gly	Val	Tyr	Thr	Lys	Val	Ser	Ala	Tyr	Leu	Asn	Trp				
			420					425							

&lt;210&gt; 219

&lt;211&gt; 556

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 219

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acaactcggt ggtggccact gcgcagacca gacttogctc gtactcgtgc gcctcgttc 60
gcttttcttc cgcaaccatg tctgacaaac ccgatatggc tgagatcgag aaattcgata 120
agtcgaaact gaagaagaca gagacgCaag agaaaaatcc actgccttcc aaagaaacga 180

```



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ttgaacagga gaagcaagca ggcgaatcgt aatgaggcgt ggcgcgccaa tatgcactgt 240
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caaagagggt ggatcaagtt taaatgactg tgctgccctt ttcacatcaa agaactactg 360
acaacgaagg ccgcgctgcc tttcccatct gtctatctat ctggctggca ggggaaggaaa 420
gaacttgcct gttggtgaag gaagaagtgg ggtggaagaa gtgggggtggg acgacagtga 480
aatctagagt aaaaccaagc tggcccaagt gtcctgcagg ctgtaatgca gtttaatcag 540
agtgccattt tttttt 556

```

&lt;210&gt; 220

&lt;211&gt; 44

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 220

```

Met Ser Asp Lys Pro Asp Met Ala Glu Ile Glu Lys Phe Asp Lys Ser
 1             5             10             15
Lys Leu Lys Lys Thr Glu Thr Gln Glu Lys Asn Pro Leu Pro Ser Lys
             20             25             30
Glu Thr Ile Glu Gln Glu Lys Gln Ala Gly Glu Ser
             35             40

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&lt;210&gt; 221

&lt;211&gt; 4792

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 221

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ggaccaccca gtaccgatcc cttcacgacc gtcaccatgg aagtgtcacc attgcagcct 60
gtaaatgaaa atatgcaagt caacaaaata aagaaaaatg aagatgctaa gaaaagactg 120
tctgttgaaa gaatctatca aaagaaaaca caattggaac atattttgct ccgcccagac 180
acctacattg gttctgtgga attagtgacc cagcaaatgt gggtttacga tgaagatgtt 240
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ctagttaatg ctgcggaaca caaacaagg gacccaaaaa tgtcttgtat tagagtcaca 360
attgatccgg aaaacaattt aattagtata tggaaataat gaaaaggat tctgttgtt 420
gaacacaaaag ttgaaaagat gtatgtccca gctctcatat ttggacagct cctaacttct 480
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&lt;210&gt; 222

&lt;211&gt; 1531

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 222

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Met Glu Val Ser Pro Leu Gln Pro Val Asn Glu Asn Met Gln Val Asn
1           5           10          15
Lys Ile Lys Lys Asn Glu Asp Ala Lys Lys Arg Leu Ser Val Glu Arg

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Ser	His	Lys	Gln	Ile	Met	Glu	Asn	Ala	Glu	Ile	Asn	Asn	Ile	Ile	Lys
			500					505					510		
Ile	Val	Gly	Leu	Gln	Tyr	Lys	Lys	Asn	Tyr	Glu	Asp	Glu	Asp	Ser	Leu
		515					520					525			
Lys	Thr	Leu	Arg	Tyr	Gly	Lys	Ile	Met	Ile	Met	Thr	Asp	Gln	Asp	Gln
		530				535					540				
Asp	Gly	Ser	His	Ile	Lys	Gly	Leu	Leu	Ile	Asn	Phe	Ile	His	His	Asn
545					550					555					560
Trp	Pro	Ser	Leu	Leu	Arg	His	Arg	Phe	Leu	Glu	Glu	Phe	Ile	Thr	Pro
			565						570					575	
Ile	Val	Lys	Val	Ser	Lys	Asn	Lys	Gln	Glu	Met	Ala	Phe	Tyr	Ser	Leu
			580					585					590		
Pro	Glu	Phe	Glu	Glu	Trp	Lys	Ser	Ser	Thr	Pro	Asn	His	Lys	Lys	Trp
		595					600					605			
Lys	Val	Lys	Tyr	Tyr	Lys	Gly	Leu	Gly	Thr	Ser	Thr	Ser	Lys	Glu	Ala
		610				615					620				
Lys	Glu	Tyr	Phe	Ala	Asp	Met	Lys	Arg	His	Arg	Ile	Gln	Phe	Lys	Tyr
625					630					635					640
Ser	Gly	Pro	Glu	Asp	Asp	Ala	Ala	Ile	Ser	Leu	Ala	Phe	Ser	Lys	Lys
				645					650					655	
Gln	Ile	Asp	Asp	Arg	Lys	Glu	Trp	Leu	Thr	Asn	Phe	Met	Glu	Asp	Arg
			660					665					670		
Arg	Gln	Arg	Lys	Leu	Leu	Gly	Leu	Pro	Glu	Asp	Tyr	Leu	Tyr	Gly	Gln
		675					680					685			
Thr	Thr	Thr	Tyr	Leu	Thr	Tyr	Asn	Asp	Phe	Ile	Asn	Lys	Glu	Leu	Ile
		690				695					700				
Leu	Phe	Ser	Asn	Ser	Asp	Asn	Glu	Arg	Ser	Ile	Pro	Ser	Met	Val	Asp
705					710					715					720
Gly	Leu	Lys	Pro	Gly	Gln	Arg	Lys	Val	Leu	Phe	Thr	Cys	Phe	Lys	Arg
				725					730					735	
Asn	Asp	Lys	Arg	Glu	Val	Lys	Val	Ala	Gln	Leu	Ala	Gly	Ser	Val	Ala
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Glu	Met	Ser	Ser	Tyr	His	His	Gly	Glu	Met	Ser	Leu	Met	Met	Thr	Ile
		755					760					765			
Ile	Asn	Leu	Ala	Gln	Asn	Phe	Val	Gly	Ser	Asn	Asn	Leu	Asn	Leu	Leu
		770				775					780				
Gln	Pro	Ile	Gly	Gln	Phe	Gly	Thr	Arg	Leu	His	Gly	Gly	Lys	Asp	Ser
785					790					795					800
Ala	Ser	Pro	Arg	Tyr	Ile	Phe	Thr	Met	Leu	Ser	Ser	Leu	Ala	Arg	Leu
				805					810					815	
Leu	Phe	Pro	Pro	Lys	Asp	Asp	His	Thr	Leu	Lys	Phe	Leu	Tyr	Asp	Asp
			820					825					830		
Asn	Gln	Arg	Val	Glu	Pro	Glu	Trp	Tyr	Ile	Pro	Ile	Ile	Pro	Met	Val
			835				840					845			
Leu	Ile	Asn	Gly	Ala	Glu	Gly	Ile	Gly	Thr	Gly	Trp	Ser	Cys	Lys	Ile
		850				855					860				
Pro	Asn	Phe	Asp	Val	Arg	Glu	Ile	Val	Asn	Asn	Ile	Arg	Arg	Leu	Met
865					870					875					880
Asp	Gly	Glu	Glu	Pro	Leu	Pro	Met	Leu	Pro	Ser	Tyr	Lys	Asn	Phe	Lys
				885					890					895	
Gly	Thr	Ile	Glu	Glu	Leu	Ala	Pro	Asn	Gln	Tyr	Val	Ile	Ser	Gly	Glu
			900					905					910		
Val	Ala	Ile	Leu	Asn	Ser	Thr	Thr	Ile	Glu	Ile	Ser	Glu	Leu	Pro	Val
			915					920					925		
Arg	Thr	Trp	Thr	Gln	Thr	Tyr	Lys	Glu	Gln	Val	Leu	Glu	Pro	Met	Leu
		930				935					940				
Asn	Gly	Thr	Glu	Lys	Thr	Pro	Pro	Leu	Ile	Thr	Asp	Tyr	Arg	Glu	Tyr
945					950					955					960
His	Thr	Asp	Thr	Thr	Val	Lys	Phe	Val	Val	Lys	Met	Thr	Glu	Glu	Lys

				965					970					975		
Leu	Ala	Glu	Ala	Glu	Arg	Val	Gly	Leu	His	Lys	Val	Phe	Lys	Leu	Gln	
			980					985					990			
Thr	Ser	Leu	Thr	Cys	Asn	Ser	Met	Val	Leu	Phe	Asp	His	Val	Gly	Cys	
		995					1000					1005				
Leu	Lys	Lys	Tyr	Asp	Thr	Val	Leu	Asp	Ile	Leu	Arg	Asp	Phe	Phe	Glu	
	1010					1015					1020					
Leu	Arg	Leu	Lys	Tyr	Tyr	Gly	Leu	Arg	Lys	Glu	Trp	Leu	Leu	Gly	Met	
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Glu	Lys	Ile	Asp	Gly	Lys	Ile	Ile	Ile	Glu	Asn	Lys	Pro	Lys	Lys	Glu	
			1060					1065					1070			
Leu	Ile	Lys	Val	Leu	Ile	Gln	Arg	Gly	Tyr	Asp	Ser	Asp	Pro	Val	Lys	
	1075						1080					1085				
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	1090					1095					1100					
Glu	Ser	Asp	Asn	Glu	Lys	Glu	Thr	Glu	Lys	Ser	Asp	Ser	Val	Thr	Asp	
1105					1110					1115					1120	
Ser	Gly	Pro	Thr	Phe	Asn	Tyr	Leu	Leu	Asp	Met	Pro	Leu	Trp	Tyr	Leu	
				1125					1130					1135		
Thr	Lys	Glu	Lys	Lys	Asp	Glu	Leu	Cys	Arg	Leu	Arg	Asn	Glu	Lys	Glu	
			1140					1145					1150			
Gln	Glu	Leu	Asp	Thr	Leu	Lys	Arg	Lys	Ser	Pro	Ser	Asp	Leu	Trp	Lys	
			1155				1160					1165				
Glu	Asp	Leu	Ala	Thr	Phe	Ile	Glu	Glu	Leu	Glu	Ala	Val	Glu	Ala	Lys	
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Glu	Lys	Gln	Asp	Glu	Gln	Val	Gly	Leu	Pro	Gly	Lys	Gly	Gly	Lys	Ala	
1185					1190					1195					1200	
Lys	Gly	Lys	Lys	Thr	Gln	Met	Ala	Glu	Val	Leu	Pro	Ser	Pro	Arg	Gly	
			1205						1210					1215		
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			1220					1225					1230			
Lys	Lys	Asn	Lys	Lys	Lys	Ile	Lys	Asn	Glu	Asn	Thr	Glu	Gly	Ser	Pro	
		1235					1240					1245				
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	1250				1255						1260					
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1265					1270					1275					1280	
Ala	Phe	Lys	Pro	Ile	Lys	Lys	Gly	Lys	Lys	Arg	Asn	Pro	Trp	Pro	Asp	
				1285					1290					1295		
Ser	Glu	Ser	Asp	Arg	Ser	Ser	Asp	Glu	Ser	Asn	Phe	Asp	Val</			

Thr Lys Arg Asp Pro Ala Leu Asn Ser Gly Val Ser Gln Lys Pro Asp  
 1445 1450 1455  
 Pro Ala Lys Thr Lys Asn Arg Arg Lys Arg Lys Pro Ser Thr Ser Asp  
 1460 1465 1470  
 Asp Ser Asp Ser Asn Phe Glu Lys Ile Val Ser Lys Ala Val Thr Ser  
 1475 1480 1485  
 Lys Lys Ser Lys Gly Glu Ser Asp Asp Phe His Met Asp Phe Asp Ser  
 1490 1495 1500  
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 1505 1510 1515 1520  
 Tyr Leu Glu Glu Ser Asp Glu Asp Asp Leu Phe  
 1525 1530

&lt;210&gt; 223

&lt;211&gt; 1111

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 223

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&lt;210&gt; 224

&lt;211&gt; 284

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 224

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 Asn Ala Leu Asp Arg Ala Glu Gln Ala Glu Ala Asp Lys Lys Ala Ala  
 20 25 30  
 Glu Asp Arg Ser Lys Gln Leu Glu Asp Glu Leu Val Ser Leu Gln Lys  
 35 40 45  
 Lys Leu Lys Gly Thr Glu Asp Glu Leu Asp Lys Tyr Ser Glu Ala Leu  
 50 55 60  
 Lys Asp Ala Gln Glu Lys Leu Glu Leu Ala Glu Lys Lys Ala Thr Asp  
 65 70 75 80  
 Ala Glu Ala Asp Val Ala Ser Leu Asn Arg Arg Ile Gln Leu Val Glu  
 85 90 95  
 Glu Glu Leu Asp Arg Ala Gln Glu Arg Leu Ala Thr Ala Leu Gln Lys

100	105	110
Leu Glu Glu Ala Glu Lys Ala Ala Asp Glu Ser Glu Arg Gly Met Lys		
115	120	125
Val Ile Glu Ser Arg Ala Gln Lys Asp Glu Glu Lys Met Glu Ile Gln		
130	135	140
Glu Ile Gln Leu Lys Glu Ala Lys His Ile Ala Glu Asp Ala Asp Arg		
145	150	155
Lys Tyr Glu Glu Val Ala Arg Lys Leu Val Ile Ile Glu Ser Asp Leu		
165	170	175
Glu Arg Ala Glu Glu Arg Ala Glu Leu Ser Glu Gly Lys Cys Ala Glu		
180	185	190
Leu Glu Glu Glu Leu Lys Thr Val Thr Asn Asn Leu Lys Ser Leu Glu		
195	200	205
Ala Gln Ala Glu Lys Tyr Ser Gln Lys Glu Asp Arg Tyr Glu Glu Glu		
210	215	220
Ile Lys Val Leu Ser Asp Lys Leu Lys Glu Ala Glu Thr Arg Ala Glu		
225	230	235
Phe Ala Glu Arg Ser Val Thr Lys Leu Glu Lys Ser Ile Asp Asp Leu		
245	250	255
Glu Asp Glu Leu Tyr Ala Gln Lys Leu Lys Tyr Lys Ala Ile Ser Glu		
260	265	270
Glu Leu Asp His Ala Leu Asn Asp Met Thr Ser Ile		
275	280	

&lt;210&gt; 225

&lt;211&gt; 501

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 225

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aacttgattt tttttattta caaaatataa atatgaagac ataaccagtt gccatctgcy 480
tgacaataaa cattatgcta a                                     501

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&lt;210&gt; 226

&lt;211&gt; 105

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 226

Met Val Lys Gln Ile Glu Ser Lys Thr Ala Phe Gln Glu Ala Leu Asp	
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Ala Ala Gly Asp Lys Leu Val Val Val Asp Phe Ser Ala Thr Trp Cys	
20 25 30	
Gly Pro Cys Lys Met Ile Asn Pro Phe Phe His Ser Leu Ser Glu Lys	
35 40 45	
Tyr Ser Asn Val Ile Phe Leu Glu Val Asp Val Asp Cys Gln Asp	
50 55 60	
Val Ala Ser Glu Cys Glu Val Lys Cys Thr Pro Thr Phe Gln Phe Phe	
65 70 75 80	
Lys Lys Gly Gln Lys Val Gly Glu Phe Ser Gly Ala Asn Lys Glu Lys	
85 90 95	

Leu Glu Ala Thr Ile Asn Glu Leu Val  
100 105

<210> 227  
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<212> DNA  
<213> Homo sapiens

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aaa 783

<210> 228  
<211> 179  
<212> PRT  
<213> Homo sapiens

<400> 228  
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20 25 30  
Lys Arg Leu Gln Gln Glu Leu Met Thr Leu Met Met Ser Gly Asp Lys  
35 40 45  
Gly Ile Ser Ala Phe Pro Glu Ser Asp Asn Leu Phe Lys Trp Val Gly  
50 55 60  
Thr Ile His Gly Ala Ala Gly Thr Val Tyr Glu Asp Leu Arg Tyr Lys  
65 70 75 80  
Leu Ser Leu Glu Phe Pro Ser Gly Tyr Pro Tyr Asn Ala Pro Thr Val  
85 90 95  
Lys Phe Leu Thr Pro Cys Tyr His Pro Asn Val Asp Thr Gln Gly Asn  
100 105 110  
Ile Cys Leu Asp Ile Leu Lys Glu Lys Trp Ser Ala Leu Tyr Asp Val  
115 120 125  
Arg Thr Ile Leu Leu Ser Ile Gln Ser Leu Leu Gly Glu Pro Asn Ile  
130 135 140  
Asp Ser Pro Leu Asn Thr His Ala Ala Glu Leu Trp Lys Asn Pro Thr  
145 150 155 160  
Ala Phe Lys Lys Tyr Leu Gln Glu Thr Tyr Ser Lys Gln Val Thr Ser  
165 170 175  
Gln Glu Pro

<210> 229  
<211> 777



&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 229

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&lt;210&gt; 230

&lt;211&gt; 165

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 230

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Met Ala Pro Asn Ala Ser Cys Leu Cys Val His Val Arg Ser Glu Glu
1          5          10          15
Trp Asp Leu Met Thr Phe Asp Ala Asn Pro Tyr Asp Ser Val Lys Lys
20        25        30
Ile Lys Glu His Val Arg Ser Lys Thr Lys Val Pro Val Gln Asp Gln
35        40        45
Val Leu Leu Leu Gly Ser Lys Ile Leu Lys Pro Arg Arg Ser Leu Ser
50        55        60
Ser Tyr Gly Ile Asp Lys Glu Lys Thr Ile His Leu Thr Leu Lys Val
65        70        75        80
Val Lys Pro Ser Asp Glu Glu Leu Pro Leu Phe Leu Val Glu Ser Gly
85        90        95
Asp Glu Ala Lys Arg His Leu Leu Gln Val Arg Arg Ser Ser Ser Val
100       105       110
Ala Gln Val Lys Ala Met Ile Glu Thr Lys Thr Gly Ile Ile Pro Glu
115      120      125
Thr Gln Ile Val Thr Cys Asn Gly Lys Arg Leu Glu Asp Gly Lys Met
130      135      140
Met Ala Asp Tyr Gly Ile Arg Lys Gly Asn Leu Leu Phe Leu Ala Ser
145      150      155      160
Tyr Cys Ile Gly Gly
165

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&lt;210&gt; 231

&lt;211&gt; 4797

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 231

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ttctacaagc agtatccaag gggccgtgta tgttcaggga tgtttccata gacttctctc 180
aagaggaatg ggaatgcctg gacgctgatc agatgaattt atacaaagaa gtgatgttgg 240
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&lt;210&gt; 232

&lt;211&gt; 433

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; VARIANT

&lt;222&gt; 433

&lt;223&gt; Xaa = Any Amino Acid

&lt;400&gt; 232

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20          25          30
Gly Pro Val Met Phe Arg Asp Val Ser Ile Asp Phe Ser Gln Glu Glu
35          40          45
Trp Glu Cys Leu Asp Ala Asp Gln Met Asn Leu Tyr Lys Glu Val Met
50          55          60
Leu Glu Asn Phe Ser Asn Leu Val Ser Val Gly Leu Ser Asn Ser Lys
65          70          75          80
Pro Ala Val Ile Ser Leu Leu Glu Gln Gly Lys Glu Pro Trp Met Val
85          90          95
Asp Arg Glu Leu Thr Arg Gly Leu Cys Ser Asp Leu Glu Ser Met Cys
100         105         110
Glu Thr Lys Ile Leu Ser Leu Lys Lys Arg His Phe Ser Gln Val Ile
115         120         125
Ile Thr Arg Glu Asp Met Ser Thr Phe Ile Gln Pro Thr Phe Leu Ile
130         135         140
Pro Pro Gln Lys Thr Met Ser Glu Glu Lys Pro Trp Glu Cys Lys Ile
145         150         155         160
Cys Gly Lys Thr Phe Asn Gln Asn Ser Gln Phe Ile Gln His Gln Arg
165         170         175
Ile His Phe Gly Glu Lys His Tyr Glu Ser Lys Glu Tyr Gly Lys Ser
180         185         190
Phe Ser Arg Gly Ser Leu Val Thr Arg His Gln Arg Ile His Thr Gly
195         200         205
Lys Lys Pro Tyr Glu Cys Lys Glu Cys Gly Lys Ala Phe Ser Cys Ser
210         215         220
Ser Tyr Phe Ser Gln His Gln Arg Ile His Thr Gly Glu Lys Pro Tyr
225         230         235         240
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<210> 233
<211> 1860
<212> DNA
<213> Homo sapiens
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<210> 234

<211> 501

<212> PRT

<213> Homo sapiens

<400> 234

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			20					25					30		
Pro	Arg	Arg	Pro	Ala	Ser	Thr	Ala	Gly	Ser	Ala	Pro	Phe	Pro	Glu	Gly
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Trp	Met	Met	Gly	Cys	Phe	Ala	Leu	Gln	Thr	Val	Asp	Thr	Glu	Leu	Thr
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Ala	Asp	Ser	Val	Glu	Trp	Cys	Pro	Leu	Gln	Gly	Cys	Arg	His	Leu	Leu
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Pro	Gln	Asn	Lys	Gly	Gly	Met	Glu	Val	Lys	Glu	Pro	Gln	Val	Arg	Leu
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His	Val	Leu	Glu	Pro	Leu	Ser	Ser	Leu	Ala	Leu	Glu	Glu	Gln	Cys	Leu
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Ala	Leu	Ser	Leu	Asp	Trp	Ser	Thr	Gly	Lys	Thr	Gly	Arg	Ala	Gly	Asp
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210						215					220				
Leu	Met	Val	Asn	Glu	Thr	Arg	Pro	Arg	Leu	Gln	Lys	Val	Ala	Ser	Trp
225					230					235					240
Gln	Ala	His	Gln	Phe	Glu	Ala	Trp	Ile	Ala	Ala	Phe	Asn	Tyr	Trp	His
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290						295					300				
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305					310					315					320
Met	Lys	Gln	Pro	Leu	Ala	Asp	Thr	Pro	Val	Gln	Gly	Gly	Val	Trp	Arg
				325					330					335	
Ile	Lys	Trp	His	Pro	Phe	His	His	His	Leu	Leu	Leu	Ala	Ala	Cys	Met
			340					345					350		
His	Ser	Gly	Phe	Lys	Ile	Leu	Asn	Cys	Gln	Lys	Ala	Met	Glu	Glu	Arg
			355				360					365			

Gln Glu Ala Thr Val Leu Thr Ser His Thr Leu Pro Asp Ser Leu Val  
 370 375 380  
 Tyr Gly Ala Asp Trp Ser Trp Leu Leu Phe Arg Ser Leu Gln Arg Ala  
 385 390 395 400  
 Pro Ser Trp Ser Phe Pro Ser Asn Leu Gly Thr Lys Thr Ala Asp Leu  
 405 410 415  
 Lys Gly Ala Ser Glu Leu Pro Thr Pro Cys His Glu Cys Arg Glu Asp  
 420 425 430  
 Asn Asp Gly Glu Gly His Ala Arg Pro Gln Ser Gly Met Lys Pro Leu  
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 Thr Glu Gly Met Arg Lys Asn Gly Thr Trp Leu Gln Ala Thr Ala Ala  
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 485 490 495  
 Glu Trp Glu Gly Asn  
 500

&lt;210&gt; 235

&lt;211&gt; 1614

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 235

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 accatttatc atggatgaaa gagatctgta aaacctgccc aggaacttac agaatttact 1140  
 ttgcagaagc gttatcatat tccatttaca tctgtgttac acgtgatctg cttaccaagc 1200  
 atattaggaa atacctctta ggaagcatta gcggtctcag gccaatfact gtggagcagc 1260  
 tttcattcct acccaacttg aaaccttggc gctgttgtct gagattgctg cagccattct 1320  
 tgttaccatg gtacttctca aactttgtga aaacctgcac ttttcttgat atgacagggt 1380  
 cctgtcttgt ctgtcatggg agccattctg ccaattttaa tgcgactgtg gtataaacag 1440  
 taaaatgatt taaaagtaag tcattccgtt tttattaatt tactgttaag tcatgttctc 1500  
 atgctcagat cagtagtgct agccagagct ttctctgcag acatgtagga agtgggtagc 1560  
 tatttttccc actccatgta ttagagtttt acaaaaaggc ttacttttga gaca 1614

&lt;210&gt; 236

&lt;211&gt; 247

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 236

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Met Ser Gly Lys Asp Arg Ile Glu Ile Phe Pro Ser Arg Met Ala Gln
 1           5           10           15
Thr Ile Met Lys Ala Arg Leu Lys Gly Ala Gln Thr Gly Arg Asn Leu
      20           25           30
Leu Lys Lys Lys Ser Asp Ala Leu Thr Leu Arg Phe Arg Gln Ile Leu
      35           40           45
Lys Lys Ile Ile Glu Thr Lys Met Leu Met Gly Glu Val Met Arg Glu
      50           55           60
Ala Ala Phe Ser Leu Ala Glu Ala Lys Phe Thr Ala Gly Asp Phe Ser
65           70           75           80
Thr Thr Val Ile Gln Asn Val Asn Lys Ala Gln Val Lys Ile Arg Ala
      85           90           95
Lys Lys Asp Asn Val Ala Gly Val Thr Leu Pro Val Phe Glu His Tyr
      100          105          110
His Glu Gly Thr Asp Ser Tyr Glu Leu Thr Gly Leu Ala Arg Gly Gly
      115          120          125
Glu Gln Leu Ala Lys Leu Lys Arg Asn Tyr Ala Lys Ala Val Glu Leu
      130          135          140
Leu Val Glu Leu Ala Ser Leu Gln Thr Ser Phe Val Thr Leu Asp Glu
145          150          155          160
Ala Ile Lys Ile Thr Asn Arg Arg Val Asn Ala Ile Glu His Val Ile
      165          170          175
Ile Pro Arg Ile Glu Arg Thr Leu Ala Tyr Ile Ile Thr Glu Leu Asp
      180          185          190
Glu Arg Glu Arg Glu Glu Phe Tyr Arg Leu Lys Lys Ile Gln Glu Lys
      195          200          205
Lys Lys Ile Leu Lys Glu Lys Ser Glu Lys Asp Leu Glu Gln Arg Arg
      210          215          220
Ala Ala Gly Glu Val Leu Glu Pro Ala Asn Leu Leu Ala Glu Glu Lys
225          230          235          240
Asp Glu Asp Leu Leu Phe Glu
      245

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&lt;210&gt; 237

&lt;211&gt; 1658

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 237

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ggcacgagct cggctcctgg aaagatggag gcagcggaga cagaggcgga agctgcagcc 60
ctagaggtcc tggctgaggt ggcaggcatc ttggaacctg taggcctgca ggaggaggca 120
gaactgccag ccaagatcct ggttgagttt gtggtggact ctcagaagaa agacaagctg 180
ctctgcagcc agcttcaggt agcggatttc ctgcagaaca tcctggctca ggaggacact 240
gctaagggtc tgcaccctt ggcttctgaa gacacgagcc gacagaaggc aattgcagct 300
aaggaacaat ggaaagagct gaaggccacc tacaggggagc acgtagaggc catcaaaatt 360
ggcctcacca aggccttgac tcagatggag gaagccaga ggaaacggac acaactccgg 420
gaagcctttg agcagctcca ggccaagaaa caaatggcca tggagaaacg cagagcagtc 480
cagaaccagt ggcagctaca acaggagaag catctgcagc atctggcgga ggtttctgca 540
gaggtgaggg agcgtaaagc agggactcag caggagcttg acgggtgtt tcagaaactt 600
ggaaacctga agcagcaggc agaacaggag cgggacaagc tgcagaggta tcagaccttc 660
ctccagcttc tgtataccct gcagggtaag ctgttgttcc ctgaggctga ggctgaggca 720
gagaatcttc cagatgataa accccagcag ccgactcgac cccaggagca gactacagga 780
gacaccatgg ggagagacc ttggtgtgtc ttcaaggctg ttggtctaca acctgctgga 840
gatgtaaatt tgccatgact tcctggagga cagcagcatg gagaaagatc ctagaaaagg 900
cctctgactt cctcacctc ccaaccatca ttacaggaaa gactgtgaac tcctgagttc 960
agcttgattt ctgactacat ccagcaagc tctggcatct gtggattaaa atccctggat 1020
ctctctcagt tgtgtatttg ttcattctta tatgctggca ggaacaacta ttaatacaga 1080

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tactcagaag ccaataacat gacaggagct gggactgggt tgaacacagg gtgtgcagat 1140
ggggaggggg tactggcctt gggcctccta tgatgcagac atgggtgaatt taattcaagg 1200
aggaggagaa tgtttttaggc aggtgggttat atgtgggaag ataattttat tcatggatcc 1260
aaatgtttgt tgagtccttt ctttgtgcta aggttcttgc ggtgaaccag aattataaca 1320
gtgagctcat ctgactgttt taggatgtac agcctagtgt taacattctt ggtatctttt 1380
tgtgccttat ctaaaacatt tctcgatcac tggtttcaga tgttcattta ttatattctt 1440
ttcaaagatt cagagattgg cttttgtcat ccactattgt atgttttgtt tcattgacct 1500
ctagtgatac cttgatcttt cccactttct gttttcggat tggagaagat gtaccttttt 1560
tgtcaactct tacttttata agatgatcaa ctcacgtatt tggatcttta tttgttttct 1620
caaataaata ttttaaggta aaaaaaaaaa aaaaaaaa 1658

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&lt;210&gt; 238

&lt;211&gt; 277

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 238

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Met Glu Ala Ala Glu Thr Glu Ala Glu Ala Ala Ala Leu Glu Val Leu
 1          5          10          15
Ala Glu Val Ala Gly Ile Leu Glu Pro Val Gly Leu Gln Glu Glu Ala
 20          25          30
Glu Leu Pro Ala Lys Ile Leu Val Glu Phe Val Val Asp Ser Gln Lys
 35          40          45
Lys Asp Lys Leu Leu Cys Ser Gln Leu Gln Val Ala Asp Phe Leu Gln
 50          55          60
Asn Ile Leu Ala Gln Glu Asp Thr Ala Lys Gly Leu Asp Pro Leu Ala
 65          70          75          80
Ser Glu Asp Thr Ser Arg Gln Lys Ala Ile Ala Ala Lys Glu Gln Trp
 85          90          95
Lys Glu Leu Lys Ala Thr Tyr Arg Glu His Val Glu Ala Ile Lys Ile
100          105          110
Gly Leu Thr Lys Ala Leu Thr Gln Met Glu Glu Ala Gln Arg Lys Arg
115          120          125
Thr Gln Leu Arg Glu Ala Phe Glu Gln Leu Gln Ala Lys Lys Gln Met
130          135          140
Ala Met Glu Lys Arg Arg Ala Val Gln Asn Gln Trp Gln Leu Gln Gln
145          150          155          160
Glu Lys His Leu Gln His Leu Ala Glu Val Ser Ala Glu Val Arg Glu
165          170          175
Arg Lys Thr Gly Thr Gln Gln Glu Leu Asp Gly Val Phe Gln Lys Leu
180          185          190
Gly Asn Leu Lys Gln Gln Ala Glu Gln Glu Arg Asp Lys Leu Gln Arg
195          200          205
Tyr Gln Thr Phe Leu Gln Leu Leu Tyr Thr Leu Gln Gly Lys Leu Leu
210          215          220
Phe Pro Glu Ala Glu Ala Glu Ala Glu Asn Leu Pro Asp Asp Lys Pro
225          230          235          240
Gln Gln Pro Thr Arg Pro Gln Glu Gln Ser Thr Gly Asp Thr Met Gly
245          250          255
Arg Asp Pro Gly Val Ser Phe Lys Ala Val Gly Leu Gln Pro Ala Gly
260          265          270
Asp Val Asn Leu Pro
275

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